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ORIGINAL PAPER

A new perspective for analyzing clinical characteristics of idiopathic retinal vasculitis, aneurysms, and neuroretinitis syndrome

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Abstract
Purpose We aimed to analyze the clinical characteristics of idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) syndrome. Furthermore, we aimed to correlate the number and location of retinal aneurysms with the size of retinal non-perfusion area and neovascularization.
Methods Six patients with IRVAN syndrome (1 male and 5 females, age 5–38 years) were enrolled in this study. Fundus fluorescein angiography (FFA) was used to determine the total number of retinal aneurysms, number of aneurysms within the first branch of the retinal artery, minimum distance between the non-perfusion margin and the optic disc, and the number of retinal aneurysms in each quadrant, as well as the type of neovascularization.
Results The size of the non-perfusion area was positively correlated with the total number of retinal aneurysms, the number of aneurysms within the first branch of the retinal artery, and the number of retinal aneurysms in each quadrant ($P < 0.05$). During the 5-year follow-up, one patient exhibited a dynamic change in the number and location of retinal aneurysms.
Conclusions In IRVAN syndrome, the number and location of retinal aneurysms correlate with the size of retinal non-perfusion area and type of neovascularization.

Keywords IRVAN syndrome · Ischemia · Aneurysms · Retinal vasculitis · Retinopathy

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Introduction

Idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) syndrome is a relatively rare retinal vasculitic disease that is usually seen in healthy young women. The etiology of the disease remains unclear. IRVAN is diagnosed based on three typical fundus features, including multiple aneurysmal dilatations at arterial bifurcations, retinal vasculitis, and neuroretinitis, as well as three minor fundus features, including peripheral capillary non-perfusion, retinal neovascularization, and macular exudation [1]. Persistent progression of retinal ischemia, non-perfusion of peripheral blood capillaries, retinal neovascularization, and exudates in the macular region can lead to severe vision loss [2]. Since Chang et al. [1] carefully characterized the clinical features of IRVAN in a case series of 10 patients, this syndrome has been increasingly diagnosed. Several studies have reported that the number and morphology of retinal aneurysms constantly change as a result of migratory inflammatory reactions in the retinal blood vessels [3, 4]. However, it remains to be determined whether the number and position of retinal aneurysms correlate with disease progression in IRVAN syndrome.

In this report, we examined the number of retinal aneurysms by fundus angiography (FFA) and investigated the relationship between the number and position of retinal aneurysms and the range of the retinal non-perfusion area. The purpose of this study was to analyze the clinical characteristics of IRVAN syndrome and to explore the correlation of number and location of retinal aneurysms with the size of the retinal non-perfusion area and neovascularization.

Methods

Patients

This study included six patients (12 eyes), who were diagnosed with IRVAN syndrome at the General Hospital of Chinese PLA from October 2000 to November 2013. Five patients were female, and one patient was male. The average age of the patients was 25 years (range 5–38 years). The disease duration ranged from 49 days to 5 years. No patient had a history of hypertension, diabetes, or other connective tissue diseases, such as arteritis nodosa and polyarteritis. This study was approved by the ethics committee of The General Hospital of Chinese PLA.

Of the six patients, one patient presented no symptoms and IRVAN syndrome was diagnosed by routine fundus examination. The other five patients presented with symptoms of blurred vision or progressive reduction of vision. In addition, three patients had shadowed vision and one patient reported headaches and visual field deficits.

Examination

All patients received routine ophthalmological examinations, including best corrected visual acuity examination, slit-lamp examination, and fundus examination. All patients were examined using fundus photography and fluorescein fundus angiography. Two patients received optical coherence tomography (OCT). One patient received B-scan ultrasonography.

Treatment

All patients (twelves eyes) were treated by krypton yellow laser photocoagulation. Among the study group, one patient (only one eye) underwent vitreoretinal surgery due to vitreous hemorrhage and tractional detachment of the retina. One patient received corticosteroid hormone.

Assessment

Clinical features, including type of retinal neovascularization, were analyzed in all patients. Fundus features, including the total number of aneurysms, number of aneurysms within the first branch of the retinal artery, and the number of aneurysms within each quadrant, were also analyzed in all patients. Due to optic disc neovascularization and vitreous hemorrhage, laser treatment was not performed in one eye and the number of aneurysms was not counted. The non-perfusion margin was determined by FFA examination. The non-perfusion margin that was closest to the optic disc was selected in the fundus camera photograph, and the distance between the non-perfusion margin and the optic disc was measured using the Auto Measure Distance tool of the Heidelberg Eye Explorer software built in the fundus camera. The distance of the ischemic area from the optic disc was determined by the minimum distance between the non-perfusion margin and the optic disc. We determined the correlation between the number of aneurysms and the distance between the non-perfusion margin and the optic disc. Measurements were performed by three researchers blinded to the experimental conditions.

Statistical analysis

Analyses were performed using SPSS 13.0 software (SPSS, Chicago, IL, USA). Spearman rank correlation analysis was used to analyze the correlation between the number of aneurysms and the distance between the non-perfusion margin and optic disc. Probability (P) values less than 0.05 were considered statistically significant.

Results

Fundus features

Among the six patients (12 eyes), aneurysmal dilatation on the optic nerve head and around the main branches of retinal arteries was seen in 11 eyes. For the one excluded eye, the fundus was not visualized clearly due to vitreous hemorrhage. FFA examination found extensive non-perfusion of peripheral capillaries (Fig. 1a). Retinal neovascularization was observed in the temporal field in one eye, which had six aneurysms within the first branch of the retinal artery and 23 aneurysms in the branches of the superior and inferior temporal arteries (Fig. 1b). In addition, one eye developed optic disc neovascularization and vitreous hemorrhage. Seven eyes had spot or patchy hemorrhages on the superficial retina. Hard exudates were observed around the optic disc and macular region in seven eyes. Two of these seven eyes had yellowish white hard exudates in the vitreous chamber (Fig. 1c).

Table 1 summarizes the total number of aneurysms, the number of aneurysms within the first branch of the retinal artery, and the minimum distance between the non-perfusion margin and the optic disc. We analyzed the correlation between the number of aneurysms and the distance from the non-perfusion margin to the optic disc using the Spearman rank correlation analysis. The distance from the non-perfusion margin to the optic disc was negatively correlated with the total number of aneurysms ($P < 0.05$, $r = -0.617$) (Fig. 2a) and the number of aneurysms within the first branch of the retinal artery ($P < 0.05$, $r = -0.674$) (Fig. 2b). This suggests that the range of peripheral non-perfusion area subsequently increases as the total number of retinal aneurysms increases, and the peripheral non-perfusion area becomes larger as the number of aneurysms within the first branch of the retinal artery increases.

We also analyzed the correlation between the number of aneurysms within a quadrant and the minimum distance between the non-perfusion margin within a quadrant to the optic disc. The minimum distance was negatively correlated with the number of aneurysms within a quadrant ($P < 0.05$, $r = -0.43$) (Fig. 2c). This finding suggests that the peripheral non-perfusion area within a quadrant increases as the number of aneurysms within the quadrant increases.

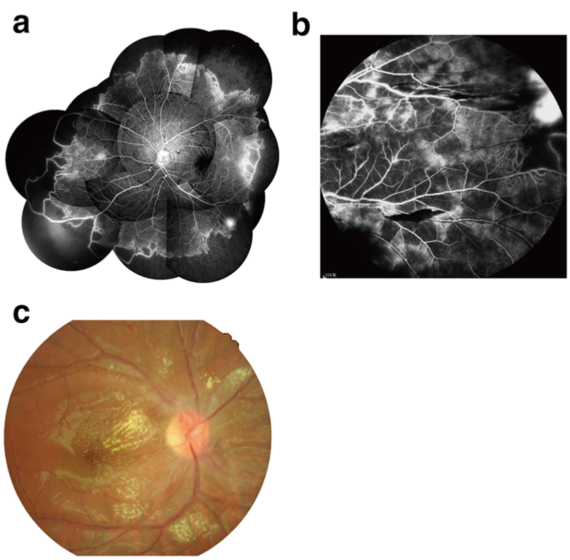

Fig. 1 **a** FFA of one patient with IRVAN syndrome, showing multiple aneurysms around the posterior retinal arterial branches and extensive capillary non-perfusion with dentate hyper-fluorescent margins. **b** FFA of one patient with IRVAN syndrome, showing neovascular membrane and non-perfusion area on the temporal side. **c** A female patient with extensive yellow hard exudates on both retinae and yellowish white hard exudates in the vitreous chamber

Treatment outcomes

All six patients (12 eyes) were treated with laser photocoagulation. In one patient with multiple aneurysms in the main branches of the retinal artery, FFA showed that new aneurysms developed along the main branches of the retinal artery during the 3-year follow-up period (Fig. 3a, b). Yellowish white exudates were observed in the macular region, which were markedly reduced after laser treatment (Fig. 3c, d). One patient had progressive non-perfusion after laser treatment at follow-up (Fig. 4); as a result, one eye underwent vitreoretinal surgery due to vitreous hemorrhage and tractional retinal detachment. One patient received corticosteroid hormone, but treatment efficacy was not obvious.

Table 1 Summary of the number of retinal aneurysms, the minimum distance between the non-perfusion margin and the optic disc, and neovascularization in patients with IRVAN syndrome

	Total number of aneurysms (right eye/left eye)	number of aneurysms within the first branch of the retinal artery (right eye/left eye)	Minimum distance between non-perfusion margin and optic disc (right eye/left eye)	Neovascularization
Case 1	2/5	2/5	9PD/8PD	None
Case 2	56/59	10/6	6PD/5PD	NVE in left eye
Case 3	1/1	1/1	7PD/7PD	None
Case 4	9/2	8/2	8PD/8PD	None
Case 5	15/12	12/12	3PD/3PD	None
Case 6	18/	11/	6PD/	NVD in left eye

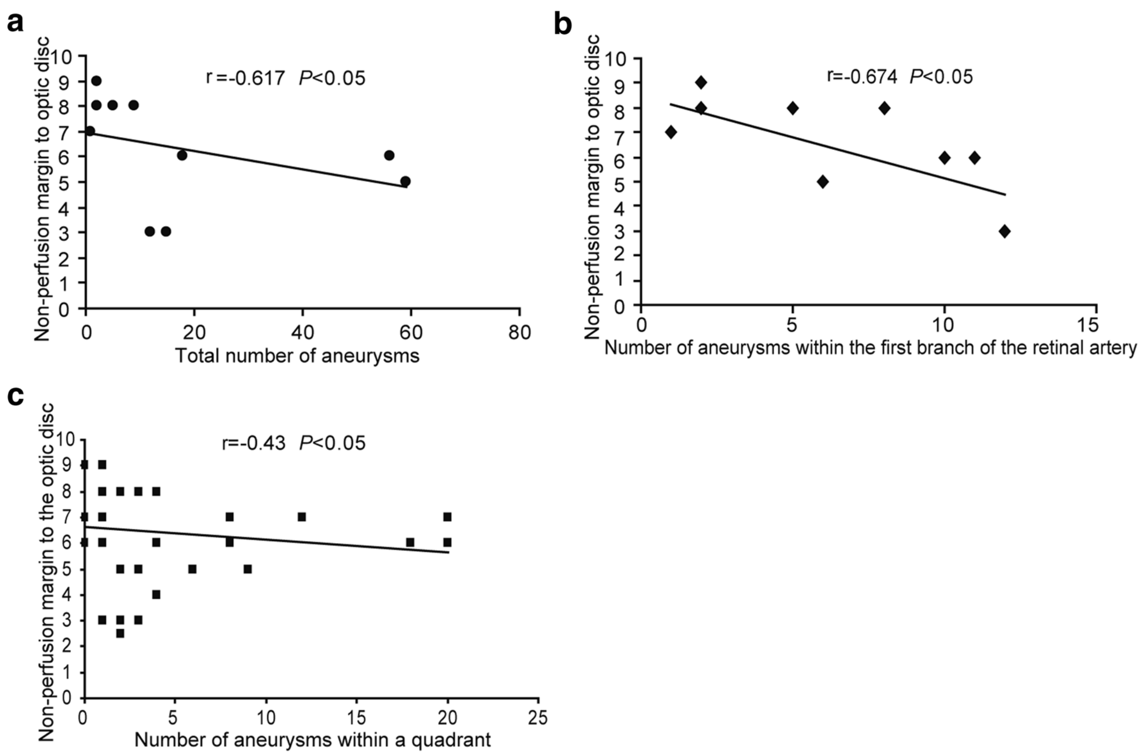

Fig. 2 **a** Negative correlation between the minimum distance from the non-perfusion margin to the optic disc and total number of aneurysms ($P < 0.05$, $r = -0.617$). **b** Negative correlation between the number of aneurysms within the first branch of the retinal artery and the minimum distance from the non-perfusion margin to the optic disc ($P < 0.05$, $r = -0.674$). **c** Negative correlation between the number of aneurysms within a quadrant and the minimum distance between the non-perfusion margin and the optic disc ($P < 0.05$, $r = -0.43$)

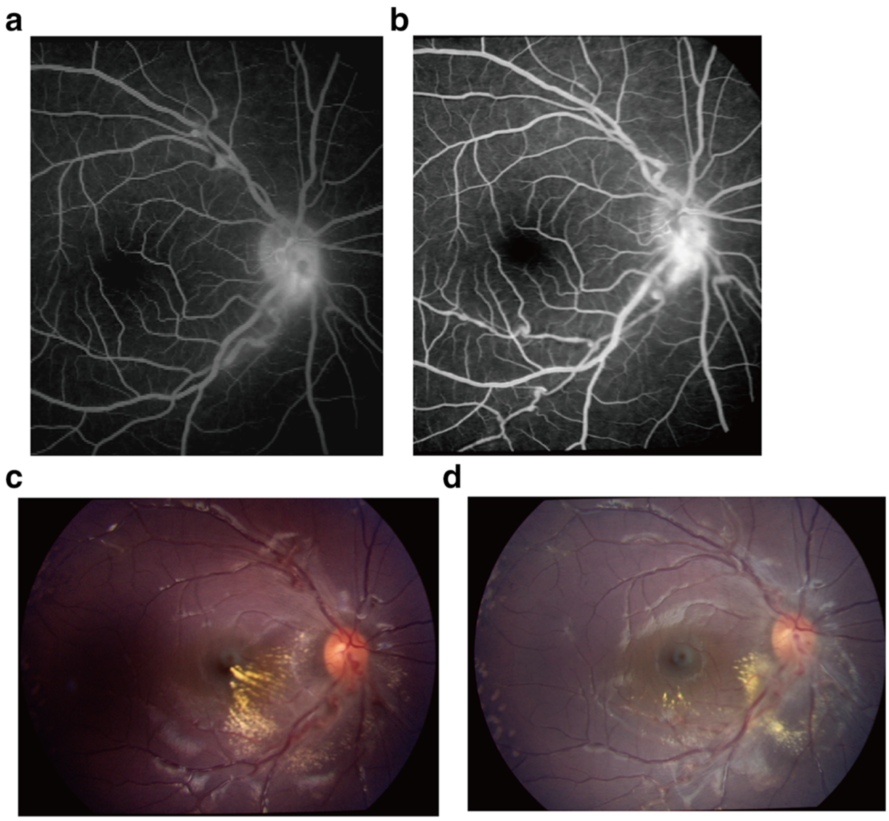

Fig. 3 Changes of aneurysms in a female patient with IRVAN syndrome. **a** FFA performed in 2002 showed multiple aneurysms around the superior temporal artery of the right eye. **b** FFA performed in 2005 showed that aneurysms around the superior temporal artery disappeared, and multiple new aneurysms developed around the inferior temporal artery. **c** Color fundus photography taken in 2002 showed yellow exudates in the macular region of the right eye. **d** Color fundus photography taken in 2005 showed remarkable reduction of yellow exudates in the macular region of the right eye (same patient)

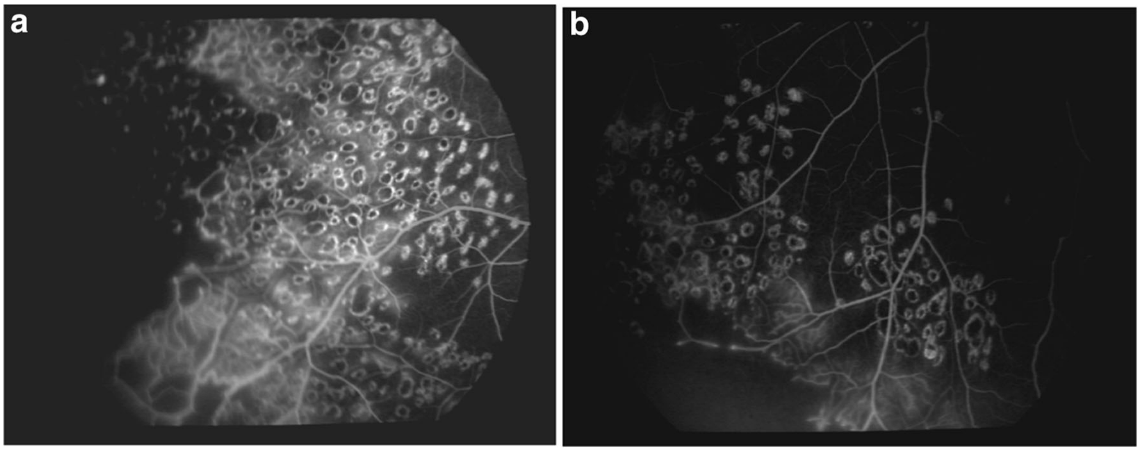

Fig. 4 A patient with IRVAN syndrome had progressive non-perfusion after laser treatment

Discussion

Fundus features of IRVAN syndrome

IRVAN syndrome is a special type of retinal vasculitis, characterized by a combination of neuroretinitis and aneurysms distributed on the posterior pole of the retina. Retinal vasculitis shares the characteristics of general vasculitis, including uneven vascular diameter, vascular white sheathing, neovascularization, fibroplasia, hemorrhagic exudation, and macular edema [5]. FFA can be used to detect uneven diameters in the retinal arteries and veins. In the late phase, FFA can also detect extensive non-perfusion of capillaries. The margin of non-perfusion area displays a corolliform or serrated appearance due to extensive arteriovenous anastomoses. Retinal ischemia may result in neovascularization in the retina and optic nerve head, vitreous hemorrhage [1], and even neovascular glaucoma [6] and tractional retinal detachment, eventually leading to severe vision loss. Sarcoidosis can cause inflammation in the retinal artery. If inflammation occurs in multiple arteries in patients with sarcoidosis, aneurysms and non-perfusion area similar to IRVAN can occur. Therefore, to correctly diagnose IRVAN, it is necessary to exclude autoimmune diseases such as sarcoidosis. In this study, five of the six symptomatic patients presented with middle or advanced stage IRVAN, with macular edema and exudation, as well as neovascularization, vitreous hemorrhage, and tractional retinal detachment. Since most patients with IRVAN syndrome in China visit the hospital in the late stage of the disease, it is important for ophthalmologists to improve understanding of this disease and manage the symptoms as soon as possible.

Development and progression of aneurysm

FFA can further detect extensive aneurysmal dilatation at the posterior pole of the retina in patients with IRVAN syndrome. Aneurysms are mainly distributed on the first and second branches of retinal arteries, particularly at the arterial junctions, due to turbulent blood flow [1]. In addition, aneurysms can be found at the optic disc arteries. Sashihara et al. [3] first reported degenerative changes of retinal aneurysms in patients with IRVAN syndrome. Yeshurun et al. conducted a six-month observational study in a patient with IRVAN syndrome and found that new aneurysms appeared after disappearance of the preexisting aneurysms. The dynamic change in the number and location of retinal aneurysms may be a result of changes in vascular wall inflammation [4]. The inflammation-affected segment of the vascular wall was dilated in response to intravascular hydrostatic pressure to form ectasia and aneurysm. With resolution of inflammation, vascular wall strength can be regained, thus, reducing the size of the aneurysm or even restoring the vessel's normal contour. Although aneurysm resolution is a part of the natural course of IRVAN and may occur without retinal laser photocoagulation [4], it remains unclear whether laser photocoagulation affects the number and location of aneurysms in patients with IRVAN during a long-term follow-up. Laser photocoagulation is used to prevent vision loss due to retinal neovascularization and is recommended for the treatment of IRVAN [5]. In this study, we found that the number and location of aneurysms correlate with ischemia in the branch of the retinal artery in IRVAN patients receiving laser photocoagulation. Further studies will be performed to investigate whether laser photocoagulation affects the number and location of aneurysms in patients with IRVAN. In this study, one patient with IRVAN syndrome had multiple aneurysms on the branches of the superior temporal artery that resolved after three years, and new aneurysms developed in the vessel wall of the branches of the inferior temporal artery, as detected by FFA. Therefore, FFA may be used to determine disease progression.

Association between the number of aneurysms and the range of non-perfusion area

In this study, we found that IRVAN syndrome severity was associated with non-perfusion area as a result of three significant correlative relationships. First, the range of non-perfusion area was positively correlated with the total number of aneurysms, which was indicative of retinal ischemia. Second, we found that the range of non-perfusion area positively correlated with the number of aneurysms within a quadrant. Third, we found that the size of non-perfusion area was positively correlated with the number of aneurysms within the first branch of the retinal artery. However, arterial hypertension aneurysms are not similar to IRVAN aneurysms. IRVAN aneurysms are generally isolated and relatively large, and have little effect on the hemodynamics of the arterial branches. Thus, ischemia is not severe and the non-perfusion area is small.

Association between the number of aneurysms and neovascularization

In patients with IRVAN syndrome, insufficient perfusion of the retinal artery results in retinal artery shrinkage and reduced blood supply to the retina, leading to the appearance of a non-perfusion area around the retina. Capillaries on the margin of the non-perfusion area compensate and develop arteriovenous anastomoses. These arteriovenous anastomoses are centered on the optic disc and are distributed around the margin of the non-perfusion area, presenting a corolliform appearance. If ischemia is not relieved, the condition becomes aggravated and the arteriovenous anastomoses fail to restore blood supply. The lack of perfusion will progressively develop until the optic disc is involved. Therefore, if vascular inflammation persists, arterial ischemia is further aggravated by retinal hypoxia, which is no longer treatable, even with laser treatment. Consistent with this idea, we found that one patient had progressive non-perfusion after laser treatment. In addition, the increased number of aneurysms within the first branch of the retinal artery indicated severe ischemia. Thus, without effective compensation, no new vessels elsewhere (NVE) will develop around the retinal non-perfusion area.

The blood supply of the optic disc blood supply is very unique. Blood supply to the capillary layer of the lamina cribrosa comes from the retinal vascular system, while the lamina cribrosa and the posterior tissues are supplied by the ciliary vascular system. Due to the rich blood supply from the choroid, the lamina cribrosa of the optic disc does not develop ischemia, thus, leading to capillary anastomosis around the optic disc and the formation of new vessels on the disc (NVD). In addition, extensive ischemia around the retina can facilitate neovascularization in the anterior segment, thus, leading to neovascular glaucoma. In this study, one eye developed NVD associated with vitreous hemorrhage and tractional retinal detachment. However, if there are less aneurysms within the first branch of the retinal artery, but more aneurysms in the second or smaller branches, the retinal blood supply can be compensated by other branches and NVE easily occurs. For example, in this study, we observed NVE in the temporal field in one case, in which there were 6 aneurysms within the first branch of the retinal artery and 23 aneurysms in the second or smaller branches of the superior and inferior temporal arteries.

Neuroretinitis

In 1977, Gass first reported that optic disc edema developed earlier than stellate exudation in the macular region in neuroretinitis, and that upon FFA the fluorescent leakage of the optic disc capillaries was caused by inflammation of blood vessels anterior to the disc lamina cribrosa [7]. Gass' study suggested that neuroretinitis was a primary disease of blood vessels in the optic disc rather than the optic nerve fibers. However, Brazis et al. argued that neuroretinitis should be named optic disc edema with a macular star (ODEMS) since the etiology was still unknown [8]. However, in a systematic literature review, Purvin et al. [9] clearly supported Gass' definition of neuroretinitis. The features of neuroretinitis in IRVAN syndrome include flush of optic nerve head with obscure boundary, macular edema and stellate exudation, and fluorescent leakage staining on the optic disc in the late phase of FFA. Fluorescent leakage is caused by aneurysms in or on the optic disc, or inflammatory leakage of the retinal arteries around the optic nerve head or on the surface of the optic disc. Such leakage may affect the structures and functions of the optic nerve fibers and even some neurons and other non-neuronal cells on the retina, thus, leading to dark spots and vision field defects. It should be noted that neuroretinitis in IRVAN syndrome is not a result of optic neuritis and retinitis. For example, neuroretinitis did not have the typical demyelinated changes and clinical features, such as inflammation in the ganglion cell axons. In this study, none of the patients presented clinical features of demyelinated optic neuritis.

Extraocular symptoms of IRVAN syndrome

Patients with IRVAN syndrome generally have no systemic diseases and no obvious abnormality upon laboratory examinations and auxiliary examinations [1]. However, the presence of perinuclear anti-neutrophil cytoplasmic antibodies has been observed in some individual cases [10]. Hammond et al. reported that an IRVAN patient who had optic disc edema and peri-disc hemorrhage in both eyes, with no brain abnormalities, presented with a high intracranial pressure of 360 mmH_2O. Thus, they suggested that retinal ischemia in IRVAN syndrome might be a consequence of intracranial hypertension and optic disc edema [11]. In addition, Abu El-Asrar et al. reported that a patient with IRVAN syndrome had nasal polyp and fungal sinusitis [12]. In the present study, all patients were seemingly healthy without a history of hypertension, diabetes or other connective tissue diseases. Only one patient showed a positive result for herpes simplex virus IgM, cytomegalovirus IgG, and rubella virus IgG. In addition, in the one patient who complained of headache, MRI examination showed multiple small ischemic lesions in the brain, but MRA showed no obvious abnormalities. Thus, the ischemic lesions were not considered to be relevant to this disease.

Conclusions

In summary, since IRVAN has a progressive course of retinal ischemia, early diagnosis and treatment with laser photocoagulation is an effective way to control disease progression and postpone neovascularization. Identification of the number and location of retinal aneurysms can help evaluate disease progression. Intravitreal injection of anti-vascular endothelial growth factor should be considered when retinal neovascularization occurs.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with 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.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

References

1. Chang TS, Aylward GW, Davis JL, Mieler WF, Oliver GL, Maberley AL et al (1995) Idiopathic retinal vasculitis, aneurysms, and neuro-retinitis. Retinal vasculitis study. Ophthalmology 102:1089–1097
2. Samuel MA, Equi RA, Chang TS, Mieler W, Jampol LM, Hay D et al (2007) Idiopathic retinitis, vasculitis, aneurysms, and neuroretinitis (IRVAN): new observations and a proposed staging system. Ophthalmology 114:1526–9 e1521
3. Sashihara H, Hayashi H, Oshima K (1999) Regression of retinal arterial aneurysms in a case of idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN). Retina 19:250–251
4. Yeshurun I, Recillas-Gispert C, Navarro-Lopez P, Arellanes-Garcia L, Cervantes-Coste G (2003) Extensive dynamics in location, shape, and size of aneurysms in a patient with idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) syndrome. Idiopathic retinal vasculitis, aneurysms, and neuroretinitis. Am J Ophthalmol 135:118–120
5. Wang Gl LuN, Wang MY (2006) Clinical feature and treatment of IRVAN syndrome. Chin Ophthalmic Res 24:191–194
6. MacIver S, Bass SJ, Sherman J (2012) Visual acuity recovery in a case of idiopathic retinal vasculitis aneurysms and neuroretinitis. Optom Vis Sci 89:E356–E363
7. Gass JD (1977) Diseases of the optic nerve that may simulate macular disease. Trans Sect Ophthalmol Am Acad Ophthalmol Otolaryngol 83:763–770
8. Brazis PW, Lee AG (1996) Optic disk edema with a macular star. Mayo Clin Proc 71:1162–1166
9. Purvin V, Sundaram S, Kawasaki A (2011) Neuroretinitis: review of the literature and new observations. J Neuroophthalmol 31:58–68
10. Nourinia R, Montahai T, Amoohashemi N, Hassanpour H, Soheilian M (2011) Idiopathic retinal vasculitis, aneurysms and neuroretinitis syndrome associated with positive perinuclear antineutrophil cytoplasmic antibody. J Ophthalmic Vis Res 6:330–333
11. Hammond MD, Ward TP, Katz B, Subramanian PS (2004) Elevated intracranial pressure associated with idiopathic retinal vasculitis, aneurysms, and neuroretinitis syndrome. J Neuroophthalmol 24:221–224
12. Abu El-Asrar AM, Jestaneiah S, Al-Serhani AM (2004) Regression of aneurysmal dilatations in a case of idiopathic retinal vasculitis, aneurysms and neuroretinitis (IRVAN) associated with allergic fungal sinusitis. Eye 18:197–199 **(discussion 199–201)**