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Optic disc edema with decreased visual function after high-altitude exposure

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Abstract

Purpose A high incidence of clinical optic disc edema has been observed at high altitudes; however, most patients experience complete regression upon returning to lowlands and do not report visual symptoms such as vision loss or visual field defects. Here, we report six patients with optic disc edema and significantly decreased visual function after high-altitude exposure.

Methods Clinical characteristics, intracranial pressure, 24-hour ambulatory blood pressure, and polysomnography data were retrospectively collected from patients presenting with optic disc edema and decreased visual function after high-altitude exposure on the Tibetan plateau between October 2020 and September 2023 at the neuro-ophthalmology department of the People's Liberation Army General Hospital in China.

Results Eleven eyes of six patients (five males and one female) were included, with a mean age of 47.3 ± 11.76 years (range 28–63). Simultaneous bilateral eye involvement was present in five of the six patients. All cases presented with diffuse disc edema at onset, which gradually resolved within 8 weeks. There was a definite time lag, ranging from 7 days to 1 month, between arrival at high altitude and symptom onset. All patients had normal intracranial pressure. Mean visual acuity was worst (20/50) at 2 weeks, and the best mean visual acuity was 20/30 at 6 months. Visual field defects were observed in all patients at the early stage of the disease, with some residual defects remaining. One patient had a small cup-to-disc ratio in the contralateral eye, while the other five could not be assessed due to bilateral optic disc edema. One patient had hypertension and severe sleep apnea; one had hypercholesterolemia and hypertension; and one had hypercholesterolemia alone.

Conclusion Optic disc edema with decreased visual function and visual field defects can occur after high-altitude exposure.

Keywords Optic disc edema, Visual function, Nonarteritic anterior ischaemic optic neuropathy, High altitude

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Introduction

In 1969, Singh et al. described four cases of optic nerve head swelling among 1925 male soldiers who had ascended to altitudes between 11,000 and 18,000 feet (3300–5500 m); this was the first report of optic disc edema at high altitude [1]. Since then, optic disc edema has been reported in mountaineers with high-altitude cerebral edema [2, 3]. Bosch et al. found that the incidence rate of optic disc swelling at very high altitudes (7546 m) is 59% [4]. Another study showed a high prevalence (79%) of clinical optic disc edema in high altitudes (4559 m) [5]. The edema is typically bilateral and is thought to be associated with cerebral edema and increased cerebrospinal fluid pressure. Almost all patients experience complete regression upon returning to low altitudes and do not report visual symptoms such as vision loss or visual field defects.

In recent years, cases of optic disc edema accompanied by decreased visual function have been reported. Most of these cases were diagnosed as monocular nonarteritic anterior ischemic optic neuropathy (NAION) occurring at high altitude. For example, a 41-year-old pilot was reported to have developed NAION in the left eye [6], and another case involved a 33-year-old man who experienced NAION for 3 months following exposure to high altitude (17,953 feet above sea level) [7]. Yin A. Liu et al. reported five patients with high-altitude-associated NAION. The main clinical characteristics of NAION include painless loss of vision associated with optic disc swelling, leading to altitudinal visual field loss and subsequent chronic optic atrophy. A small cup-to-disc ratio or small optic discs (also referred to as congenitally anomalous discs or "discs at risk") is the strongest risk factor associated with NAION (over 95%) [8, 9]. Other risk factors strongly associated with NAION include hypertension, hypercholesterolemia, diabetes mellitus, cardio- and cerebrovascular disease, and obstructive sleep apnoea [10].

Few cases have described bilateral optic disc edema with decreased visual function after high-altitude exposure. One case exhibited bilateral optic disc edema coupled with visual acuity deterioration and visual field contraction in both eyes after high-altitude exposure [11]. Another case involved intolerance to hypoxia in the occurrence of bilateral NAION at high altitude [12].

Tibet, with an average altitude above 4000 m, is often referred to as the "roof of the world," while most other regions in China are below 2000 m. As a result of its high altitude, environmental factors such as low atmospheric oxygen, low humidity, strong ultraviolet radiation, and low temperatures are prevalent. In the current study, we enrolled six patients with optic disc edema and decreased visual function following a tour on the Tibetan plateau. Five patients exhibited binocular involvement, while one patient exhibited monocular involvement [13].

Materials and methods

The clinical records of patients who presented with decreased visual function and optic disc edema following high-altitude exposure between October 2018 and September 2023 were retrospectively reviewed from the neuro-ophthalmology department of the People's Liberation Army General Hospital in China. Data collected included time from altitude exposure to symptom onset, cup-to-disc ratio, clinical characteristics, intraocular pressure, presence of sleep apnea, and 24-hour ambulatory blood pressure measurements.

The study protocol was approved by the institutional review board of the People's Liberation Army General Hospital (S2020-D09-01) and adhered to the tenets of the Declaration of Helsinki and the ICH-GCP guidelines. Written informed consent was obtained from all study participants.

Ophthalmological examinations and associated examinations

Best-corrected visual acuity was assessed using a Snellen chart and converted to logarithmic units for analysis. Visual field testing was performed using a Humphrey Field Analyzer (Carl Zeiss Meditec Inc., USA) with the Swedish Interactive Threshold Algorithm Standard 24 – 2 program and a white Goldmann size III stimulus. Patients with poor visual acuity (less than 20/200) were unable to achieve satisfactory visual field results. Optical coherence tomography (OCT) was performed using spectral-domain devices (Carl Zeiss Meditec, USA) with standard protocols for the Optic Disc Cube 200 × 200 scan and the Macular Cube 512 × 128 scan. All patients underwent optic nerve magnetic resonance imaging (MRI), which included T2-weighted imaging (T2WI) with fat suppression, T1-weighted imaging (T1WI) with fat suppression, and gadolinium-enhanced T1 imaging. Lumbar puncture was performed in all patients to measure intracranial pressure, white cell counts, and total protein levels. Serum aquaporin-4 (AQP4) antibody and myelin oligodendrocyte glycoprotein (MOG) antibody levels were assessed using cell-based assays in all patients.

Testing for risk factors associated with NAION

To identify risk factors associated with nonarteritic anterior ischemic optic neuropathy (NAION), we evaluated the following parameters: cup-to-disc ratio, blood pressure, blood glucose, glycated hemoglobin, lipid profile, 24-hour ambulatory blood pressure, and polysomnography. These factors are considered important in the pathogenesis of NAION, including small cup-to-disc ratio and small optic discs, hypertension, diabetes mellitus,

Table 1 Clinical characteristics of patients after high altitude exposure

Patients/ Sex/Age	Invloved eyes	Time of onset (After leaving HA)	VA at onset		VA at 6 month		RNFL at onset (um)		RNFL at 6 month (um)	
			OD	OS	OD	OS	OD	OS	OD	OS
1/M/46	Bilateral	HA	20/25	20/30	20/30	20/30	370	389	80	81
2/M/48	Bilateral	2 days	20/20	20/100	20/20	20/1000	143	171	66	62
3/M/44	Bilateral	2 days	20/20	20/200	20/20	20/200	159	153	77	63
4/M/28	Bilateral	HA	20/30	20/20	20/20	20/20	239	251	72	86
5/M/63	Left eye	7 days	20/20	20/25	20/20	20/20	97	210	70	74
6/F/55	Bilateral	1 days	20/20	20/60	20/40	20/40	261	282	64	57

Abbreviations: M, male; F, female; HA, high altitude area; VA, visual acuity

hypercholesterolemia, and sleep apnea. Additionally, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and autoimmune-related antibodies were assessed to exclude giant cell arteritis and other possible differential diagnoses.

Results

Clinical features

A total of six patients (five males and one female) with 11 eyes affected were included in this study. The mean age was 47.33 ± 11.76 years (range 28 to 63 years). Simultaneous bilateral eye involvement was observed in five of the six patients. The initial symptoms included visual field defects accompanied by painless vision loss. At presentation, all cases exhibited diffuse disc edema, which gradually resolved within 8 weeks. Although there was no significant excavation of the optic cup, thinning of the retinal nerve fiber layer was noted (Table 1).

A definite time lag was observed between arrival at high altitude and symptom onset, ranging from 7 days to 1 month. Specifically, two patients experienced symptom onset while staying in Tibet for 7 days and 10 days, respectively. Four patients developed symptoms after returning to low altitude, with symptom onset occurring 1 to 7 days after departure. These four patients had previously stayed in Tibet for durations ranging from 5 days to 1 month (Table 1). No enhancement of the optic nerve was observed on gadolinium-enhanced T1-weighted imaging (T1WI) in any patient. T2-weighted imaging (T2WI) did not reveal any abnormal optic nerve signals. All patients had normal intracranial pressure. Additionally, serum aquaporin-4 (AQP4) antibody and myelin oligodendrocyte glycoprotein (MOG) antibody tests were negative in all patients.

Vision acuity

At onset, the worst mean visual acuity was 20/50 at 2 weeks. Of the 11 eyes, six had visual acuity better than 20/40; four had visual acuity between 20/40 and 20/200; and one had visual acuity worse than 20/200. The best mean visual acuity was 20/30 at 6 months. Stable vision was observed in three of the 11 eyes, while eight of the

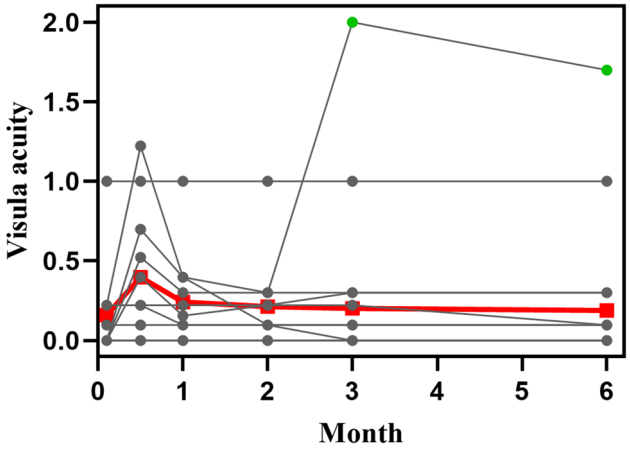

Fig. 1 Spaghetti plot showing the evolution of visual acuity (LogMAR) in 11 eyes over a 6-month period. Three eyes maintained stable visual acuity of 20/20 following disease onset. In the remaining eight eyes, vision loss worsened over several days to 2 weeks. Among these, five eyes experienced partial recovery within 1 month, two eyes showed no improvement, and one eye had a second exacerbation at 2 months (indicated by the green dot). Note: The red line represents the mean visual acuity at different time points (the two extreme values marked by green dots were excluded from the calculations)

11 eyes experienced decreased visual acuity after disease onset. Overall, visual acuity worsened over several days to 2 weeks, improved rapidly within 1 month, and then remained relatively stable with slight improvement over 6 months. One eye experienced a sudden aggravation at 2 months after onset. In this case, other potential causes for the secondary vision loss were excluded (Fig. 1).

Visual field

Visual field defects were observed in all patients at the early stage of the disease. A diffuse visual field defect was present in six of the 11 eyes, while an inferior altitudinal visual field defect was noted in three of the 11 eyes. Two eyes exhibited non-specific and mild visual field defects. Visual fields gradually improved within 3 months, with the superior visual field recovering prior to the inferior visual field. The evolution of the visual field in a 55-year-old female patient with a final visual acuity of 20/40 in both eyes is illustrated in Fig. 2(A-H). This patient had

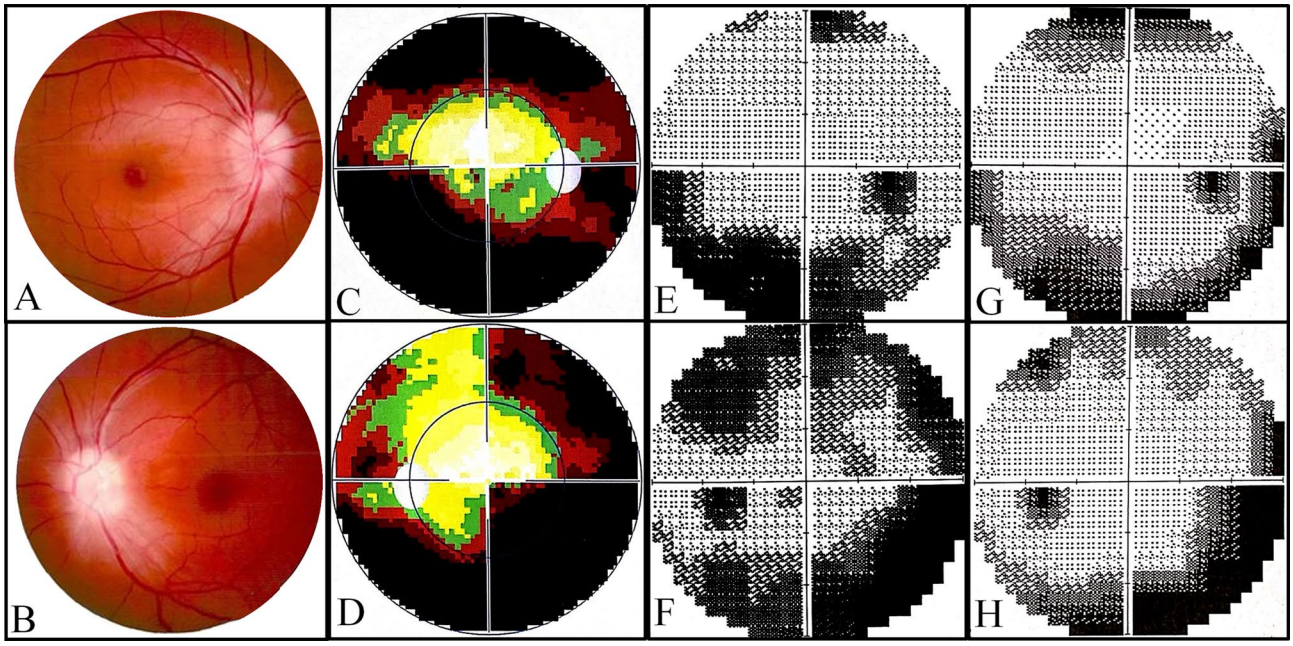

Fig. 2 Fundus photographs taken at 25 days (**A**, **B**) and visual field evolution in the right eye (**A**, **C**, **E**, **G**) and left eye (**B**, **D**, **F**, **H**) at 10 days (**C**, **D**), 50 days (**E**, **F**), and 70 days (**G H**) after disease onset, respectively. At onset, there was a diffuse peripheral visual field defect, which gradually improved to residual inferior altitudinal loss. This type of visual field defect is the most common in non-arteritic anterior ischemic optic neuropathy (NAION)

stayed in Tibet for 20 days and reported blurred vision 1 day after returning to low altitude.

Risk factors associated with NAION

We investigated risk factors that have been strongly associated with nonarteritic anterior ischemic optic neuropathy (NAION), including cup-to-disc ratio, hypertension, hypercholesterolemia, diabetes mellitus, cardiovascular and cerebrovascular disease, and obstructive sleep apnea. One patient had a small cup-to-disc ratio in the contralateral eye; cup-to-disc ratios could not be assessed in the other five patients due to bilateral optic disc edema within several weeks of onset. Among the patients, one had hypertension and severe sleep apnea, one had hypercholesterolemia and hypertension, and one had hypercholesterolemia alone. The remaining three patients had no known systemic risk factors associated with NAION.

Discussion

We report six patients with optic disc edema and obvious visual symptoms related to high-altitude exposure. Notably, five of the six patients exhibited simultaneous bilateral eye involvement. One case with monocular involvement had a cup-to-disc ratio of 0.1 in the contralateral eye, which could be diagnosed as NAION. The cup-to-disc ratios could not be assessed in the other five patients due to bilateral optic disc edema within several weeks of onset.

Previous research on the mechanism of optic disc edema has predominantly focused on high-altitude cerebral edema. Exposure to high altitudes can significantly reduce blood oxygen saturation, thereby inducing hypoxemia. This, in turn, results in a significant increase in cerebral blood flow and blood volume [14–16]. Vasogenic edema [17], hemodynamic factors such as sustained vasodilatation [18], impaired cerebral autoregulation [19], and elevated cerebral capillary pressure [20] induce brain swelling and elevated intracranial pressure. This can directly obstruct axoplasmic flow and cause papilledema. Almost all patients experience complete regression of symptoms upon returning to lowlands and do not complain of visual symptoms such as vision loss or visual field defects [5]. However, in our cohort, patients exhibited visual field defects or painless vision loss, and all had normal intracranial pressure. This makes high-altitude cerebral edema less likely to be the cause of decreased visual function following high-altitude exposure in our cohort. Nevertheless, we cannot completely exclude this possibility, as the intracranial pressure during the high-altitude period was unknown.

Moreover, Singh et al. [1] f found that acute mountain sickness typically manifests several hours after arrival at high altitude. The time lag between arrival at high altitude and the onset of symptoms suggests that there is no direct correlation between hypoxia and acute mountain sickness, and patients do not readily respond to oxygen therapy. In our study, there were significant delays between the onset of visual symptoms and high-altitude exposure: two patients developed symptoms one week after leaving Tibet, following a one-month stay there. For

the same reason, we also believe that there was no direct relationship between hypoxia and optic disc swelling in our cohort.

In previous reports on NAION occurring at high altitude, a total of eight cases all exhibited monocular involvement [6, 7, 21, 22]. However, there have been a few cases with characteristics similar to those of the patients in this cohort. ZF Liu reported one case with optic disc edema after high-altitude exposure, noting visual acuity deterioration and visual field contraction in both eyes after the patient returned to lowlands. At the initial examination, his vision acuity was 20/200 in the right eye and 20/1000 in the left eye; visual acuity returned to normal and optic disc edema disappeared after 1 month [11]. Another case was diagnosed as having bilateral NAION at high altitude [12]. Therefore, both monocular and binocular NAION can occur after high-altitude exposure, but further research is needed to determine which form is more common.

The more likely diagnosis in our study was NAION, based on the clinical characteristics: optic disc edema with decreased visual function, normal intracranial pressure, and no enhancement of the optic nerve on gadolinium-enhanced T1WI. NAION after high-altitude exposure has not been extensively described. Therefore, the cause remains obscure. Vigorous physical exercise during high-altitude exposure, combined with hypoxia during sleep, may contribute to reduced oxygen supply to the optic nerve head. Other possible factors include higher altitude, faster ascent, longer duration at high altitude, lower hematocrit, strenuous activity, and higher baseline intraocular pressure [21].

Here, we propose a hypothesis: In order to increase oxygen-carrying capacity, hypoxic responses at high altitudes trigger angiogenesis and erythropoiesis. This, in turn, leads to polycythemia and thrombocytosis, which generate hypercoagulability and microcirculation obstruction. Upon returning to normal altitude, these pathophysiological changes can have a significantly harmful impact on the terminal blood vessels—the short posterior ciliary arteries. This may result in ischemia of the short posterior ciliary arteries, leading to nonarteritic anterior ischemic optic neuropathy (NAION). This pathogenesis also explains why diffuse visual field defects are more commonly observed than inferior altitudinal losses. The superior visual field defects resolving first, along with residual inferior altitudinal loss, are consistent with the characteristics of NAION. Additionally, the gradual resolution of diffuse disc edema within 8 weeks, coupled with the absence of significant optic cup excavation despite thinning of the retinal nerve fiber layer, further support this diagnosis.Two limitations of our study should be mentioned. First, it was a retrospective analysis, so we could not determine the exact time of disc edema resolution or the state of intracranial pressure while two patients had symptoms at high altitude. Second, research on the mechanism of optic disc edema associated with high altitude has focused on the early stages of high-altitude exposure, with little illumination of ocular symptoms and signs. Why many patients developed symptoms after leaving high altitude rather than during high-altitude exposure requires further research. This study reports that optic disc edema with decreased visual function and visual field defects can occur after high-altitude exposure. We hypothesize that both monocular and binocular NAION can occur after high-altitude exposure.

Abbreviations

NAION	Nonarteritic anterior ischaemic optic neuropathy
MRI	Magnetic resonance imaging
T2WI	T2-weighted image
T1WI	T1-weighted image
PLAGH	People's Liberation Army General Hospital

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions
Design and conduct of the study by HZ and QX. Collection, analysis, management and interpretation of the data by YL and MS. Preparation of the manuscript by YL, HZ and XZ. Critical revision of the manuscript was performed by HZ and SW. Review and final approval of the manuscript by all the authors.

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Data availability
Contact to Professor Huanfen Zhou (zhouzhoueye@163.com) or Shihui Wei (weishihui706@hotmail.com).

Declarations

Ethics approval and consent to participate
This study was approved by the Chinese People's Liberation Army General Hospital Ethics Committee (S2020-D09-01) and was conducted following the Declaration of Helsinki in its currently applicable version and applicable Chinese laws. We have obtained written informed consent for this publication from all of the participants.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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