Vascular Endothelial Growth Factor as a Prognostic Parameter in Subjects with “Plateau Red Face”

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Abstract

Ma, Lan, Ying Chen, Guoen Jin, Yingzhong Yang, Qin Ga, and Ri-Li Ge. Vascular endothelial growth factor as a prognostic parameter in subjects with “plateau red face.” *High Alt Med Biol* 16:147–153, 2015.—Some individuals living at high altitude on the Qinghai Plateau in China develop a red face called “Plateau Red Face” (PRF). It is characterized by telangiectasia of the cheeks, which become a unique ruddy color. It is more common in young females than males, subjects who have polycythemia are more susceptible to PRF, and its pathogenesis is unknown. The aim of this study was to investigate associations between PRF and levels of vascular endothelial growth factor (VEGF).

Methods: A total of 158 subjects (82 male and 76 female) residing at 4300 m and 140 subjects (73 male and 67 female) residing at 2260 m on the Qinghai Plateau, China, participated in this study. The determination and magnitude of PRF is evaluated by the dilation of veins on the face in the Qinghai chronic mountain sickness (CMS) score, established during the World Congress in 2004. Arterial O₂ saturation (Sao₂), hemoglobin (Hb) concentration, pulmonary function tests, and serum concentration of VEGF (by ELISA) were measured in all participants.

Results: The occurrence of PRF was 32.9% (52/158) among subjects living at 4300 m and 15.7% (22/140) among those living at 2260 m. The levels of VEGF in PRF and non-PRF subjects were 399.9 ± 115.6 pg/mL and 270.7 ± 78.1 pg/mL, respectively ($p < 0.001$) at 4300 m, and 244.4 ± 109.0 pg/mL and 135.6 ± 65.3 pg/mL, respectively ($p < 0.01$) at 2260 m. However, comparing the levels of VEGF between the genders and ethnic groups at the same altitude, there were no significant differences between male and female both in Xining ($p = 0.12$) and Maduo ($p = 0.18$). There was also no significant difference between Tibetan and Han nationality in Xining ($p = 0.71$), but in Maduo, the levels of VEGF in Han (351.70 ± 122.62 pg/mL) were higher than that of Tibetan (300.20 ± 102.89 pg/mL), and there was significant difference ($p = 0.01$). Sao₂ levels in PRF subjects (86.58 ± 3.49) were lower than those of non-PRF subjects (88.04 ± 3.68 ; $p = 0.018$), while Hb was higher. Areas under receiver operator characteristic curve for diagnosis of PRF were 0.813, 0.679, and 0.373 for VEGF, Hb, and Sao₂, respectively. VEGF levels correlated positively with Hb levels both in Xining ($r = 0.367$, $p < 0.001$) and Maduo ($r = 0.319$, $p < 0.001$), and only negatively with Sao₂ levels in Maduo ($r = -0.424$, $P < 0.001$) but not in Xining ($r = 0.125$, $p = 0.141$).

Conclusion: Chronic hypoxemia may stimulate overproduction of angiogenic cytokine (VEGF), and this peptide may lead to formation of abnormal new vessels and development of congestion in mucosa and conjunctiva. Thus, VEGF may, at least in part, serve as a marker of the pathophysiologic trigger for PRF.

Key Words: hemoglobin; hypoxia; Plateau Red Face; VEGF

Introduction

MANY LONG-TERM RESIDENTS OF HIGH ALTITUDES, particularly subjects with excessive polycythemia, exhibit a unique, ruddy facial color, which is called “Plateau Red Face” (PRF). Its distinctive feature is telangiectasia of the cheeks, ear

edges, bridge of the nose, and the conjunctivae. This telangiectasia is the persistence of expanded small blood vessels, mostly small veins or arteries, forming a mesh-like appearance. Upon clinical observations of subjects at high altitude, it seems to be more common in females than males, but there are no epidemiological data on the exact prevalence of PRF.

Most subjects with PRF are asymptomatic other than facial redness, and there are no effects limiting physical activity or daily life. However, subjects with an extremely high concentration of Hb often suffer severe hypoxemia and exhibit expanded telangiectasia. The causes of PRF are unknown, it is generally believed that exposure to high-altitude multiple factors (West, 2012), such as hypoxia, cold temperatures, strong winds, and strong ultraviolet rays may lead to PRF due to dilation of the small blood vessels of the face (Penaloza and Arias-Stella, 2007). In this report, we hypothesize that vascular endothelial growth factor (VEGF), as a key mediator of angiogenesis (Tissot et al. 2005), may be associated with the formation of PRF. VEGF is essential for angiogenesis during embryonic development, wound healing, and tumor growth, and the expression of its gene is mainly stimulated by hypoxia through mediation of hypoxia-inducible factors (HIF). HIF-mediated gene expression might take place in the development of PRF as a result of severe high-altitude hypoxia. Based on these considerations, the hypothesis of the present study is that VEGF is associated with the development of PRF.

Materials and Methods

Subjects

A total of 158 subjects (mean age 42 ± 13 years) residing at an altitude of 4300 m in Maduo, China, and 140 subjects (mean age 39 ± 14 years) residing at 2260 m in Xining, China, participated in this study. Most of the subjects in Maduo are nomads and permanently live at altitudes of 4300–5000 m, while the Xining (2260 m) subjects were mostly Han Chinese (Table 1). The research protocol was approved by the human subject protection committee at the Medical College of Qinghai University. Informed consent was obtained from each subject.

Assessment of PRF

The presence of PRF was determined by the Qinghai chronic mountain sickness (CMS) score (León-Velarde et al.,

2005). The magnitude of facial redness was determined by the examining physician (GRL) according to the ruddiness of the surface area and the dilation of veins of the cheeks, and graded as mild, moderate, or severe.

Measurements

Arterial O_2 saturation (SpO_2) was measured by pulse oximetry (Ohmeda 3700 Pulse Oximeter, Datex-Ohmeda, Boulder, CO); hemoglobin concentration (Hb) was detected by Automatic Blood Cell Analyzer (BC-2300, Shenzhen, People's Republic of China); body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2); and serum concentration of VEGF (by ELISA) was performed. All participants also underwent an ECG. Pulmonary function (PF) tests and pulmonary arterial pressure (PAP) were only performed in subjects from Maduo. PF tests were performed using a standard electric spirometer controlled by a microcomputer (Transfer Screen II: Jaeger; Wuirzburg, Germany). Lung volumes, maximal flow-volume loop, and maximal voluntary ventilation were recorded and analyzed by the Jaeger system. PAP was measured by echocardiography (Vivid i, GE Healthcare, Milwaukee, WI), including left and right ventricular function, as well as mean pulmonary artery pressure (mPAP). The mPAP was estimated from Doppler velocity recorded across the tricuspid valve, using a modification of the Bernoulli equation ($PAP = [4 \times \text{velocity}]^2 + 10 \text{ mm Hg}$).

Blood sampling and assay

A 3 mL blood sample was drawn from the brachial vein of all participants ($n=298$), collected into a serum separator tube, and allowed to sit for 15 min at $4^\circ C$ before centrifugation (3000 rpm for 10 min). Serum samples were stored in liquid nitrogen for analysis. Serum VEGF was measured with an enzyme linked immunosorbent assay (ELISA) kit (D&R system), which was described previously (Ge et al., 2011). This assay was calibrated against highly purified recombinant human VEGF 165. The measurable range of the VEGF assay was 31.2–2000 pg/mL.

TABLE 1. COMPARISON OF VARIABLES BETWEEN PLATEAU RED FACE (PRF) AND NON-PRF AT XINING AND MADUO

Variable	Xining (2260 m)			Maduo (4300 m)		
	PRF (n=22)	non-PRF (n=118)	p value	PRF (n=52)	non-PRF (n=106)	p value
Age (y)	41.04 ± 18.13	35.60 ± 12.89	0.092	33.8 ± 9.61	44.1 ± 7.9	0.001
Height (cm)	165.33 ± 7.15	166.32 ± 7.54	0.574	166.04 ± 9.06	163.44 ± 8.52	0.08
Weight (kg)	62.47 ± 13.92	62.34 ± 10.33	0.959	58.50 ± 10.90	59.07 ± 10.67	0.756
BMI (kg/cm^2)	22.63 ± 4.12	22.54 ± 3.23	0.909	21.07 ± 3.05	22.03 ± 3.24	0.076
mPAP (mmHg)	/	/	/	25.52 ± 7.05	21.11 ± 6.73	0.001
Hb (g/dL)	17.19 ± 1.82	16.00 ± 1.77	0.005	19.09 ± 2.67	17.87 ± 2.71	0.009
HR (beats/min)	78.15 ± 9.653	77.33 ± 11.09	0.756	78.56 ± 15.14	78.36 ± 11.99	0.933
SpO_2 (%)	94.86 ± 1.05	94.14 ± 1.95	0.786	86.58 ± 3.49	88.04 ± 3.68	0.018
VEGF (pg/mL)	244.37 ± 109.03	135.67 ± 65.3	0.001	399.89 ± 115.6	270.73 ± 78.12	0.001
VC	4.58 ± 0.98	5.23 ± 0.78	0.245	4.41 ± 0.77	4.23 ± 0.67	0.139
FEV ₁ %	89.45 ± 5.24	90.56 ± 5.63	0.563	88.31 ± 5.24	87.69 ± 5.43	0.491
FEF _{25–75} %	3.10 ± 0.79	3.70 ± 0.84	0.367	3.18 ± 0.59	3.30 ± 0.64	0.261
MVV	149.67 ± 28.45	154.36 ± 28.35	0.567	143.75 ± 22.04	144.36 ± 24.84	0.881

Data expressed as mean $\pm$ standard deviation unless otherwise specified; BMI, body-mass index; FEF_{25–75}%, mean forced expiratory flow during half of the forced vital capacity; FEV₁%, percent of forced expiratory volume in 1 second; Hb, hemoglobin; HR, heart rate; mPAP, mean pulmonary arterial pressure; MVV, maximal voluntary volume; SpO_2 , oxygen saturation; VEGF, vascular endothelial growth factor.

TABLE 2. GENERAL CHARACTERISTICS BETWEEN PLATEAU RED FACE (PRF) AND NON-PRF AT XINING AND MADUO

	Xining (2260 m)					Maduo (4300 m)				
	PRF (n=22)	non-PRF (n=118)	Total	X ² value	p value	PRF (n=52)	non-PRF (n=106)	Total	X ² value	p value
Male	10(45.5%)	63(53.4%)	73	0.468	0.494	30(57.7%)	52(49.1%)	82	1.042	0.307
Female	12(44.5)	55(46.6%)	67			22(42.3%)	54(50.9%)	76		
Tibetan	7(31.8%)	14(11.9%)	21	5.791	0.025	31(59.6%)	87(82.1%)	118	9.308	0.002
Han	15(68.2%)	104(88.1%)	119			21(40.4%)	19(17.9%)	40		

Statistical analysis

All measurement data were normal distribution, and the data are expressed as mean $\pm$ SD. All count data are expressed as percentage. Statistics were done using SPSS software (version 13.0; Chicago, IL). Comparison of various parameters between subject groups was made by Fisher protected least significant difference test at the 95% significant level. A Student's unpaired *t*-test was used in comparing PRF and non-PRF groups. All count data used Chi-square test. Linear regression analysis was used to assess the correlation between variables. Receiver operator characteristic (ROC) curves (Analyze-it; Leeds, UK) examined VEGF, SaO₂, and Hb values for diagnosis of PRF, with area under the curve established and expressed with 95% confidence intervals (CI). The significance level was set at $p < 0.05$.

Results

General characteristics

The clinical characteristics of subjects with and without PRF in Maduo and Xining are shown in Table 1. In Maduo, most subjects were Tibetan natives, only 40 subjects were Han Chinese. The rate of occurrence of PRF was 32.9% (52/158 at an altitude of 4300 m and 15.7% (22/140) at 2260 m. There was no significant difference in the rate of PRF between genders in both areas (Table 2). Severity of PRF in Maduo subjects: 15 of 52 subjects were mild, 21 moderate, and 16 severe. In Xining, 11 of 22 subjects were mild, 8 moderate, and 3 severe, and there were no significant differences at the two altitudes ($p = 0.15$) (Table 3).

Symptoms

Most subjects with PRF were asymptomatic, but a few severe PRF subjects, specially Han Chinese in Maduo, showed clinical symptoms such as headache, breathlessness, fatigue, sleep disturbance, and cyanosis, whereas these were absent in the Xining group.

Variables between PRF and non-PRF

Table 1 showed that there were no significant differences in vital capacity, percentage of forced expiratory volume in

1 sec, mean forced expiratory flow during the first half of the forced vital capacity (25%–75%), or maximal voluntary ventilation values between the two groups at different altitudes, suggesting that subjects with and without PRF were absent of chronic obstructive pulmonary disease.

SaO₂ levels in Maduo were lower in PRF subjects (86.58 ± 3.49) than non-PRF subjects ($88.04 \pm 3.7\%$; $p = 0.018$), but it showed no significant difference between the two groups in Xining. Hb and VEGF in the PRF groups were significantly higher than in the non-PRF groups, both in Xining and Maduo.

Multivariate regression analysis

Table 4 showed that several confounding factors, especially age, Hb, VEGF, and FEF_{25%–75%} were related to the severity of PRF. The predictors of the severity of PRF included VEGF ($\beta = 0.642$; $p < 0.0001$), Hb ($\beta = 0.116$; $p = 0.05$), age ($\beta = -0.310$; $p < 0.0001$), and FEF_{25%–75%} ($\beta = -0.118$; $p = 0.035$).

Biomarkers

Serum VEGF levels were significantly higher in the PRF group than in the non-PRF group ($p < 0.01$), both in Maduo and Xining (Fig. 1). Comparing the serum VEGF levels between Tibetan and Han nationality at different altitudes, the results showed that the VEGF levels in Maduo were significant higher than in Xining, both Tibetan group and Han group ($p < 0.001$), and it was higher in Han Chinese than Tibetan in Maduo ($p < 0.05$), but there was no significant difference in Xining ($p > 0.05$) (Fig. 2). We also compared the serum VEGF levels between male and female. The results showed that the VEGF levels in Maduo were significant higher than in Xining both in male and female ($p < 0.001$), but there were no significant differences between male and female both in Maduo and Xining ($p > 0.05$) (Fig. 3).

Correlations and ROC analyses

VEGF levels correlated positively with Hb levels both in Maduo and Xining (Figs. 4A and 5A), and negatively with SaO₂ levels in Maduo (Fig. 5B), while there was no correlation between VEGF and SaO₂ in Xining residents, and there was no significant difference (Fig. 4B). ROC analysis (Fig. 6)

TABLE 3. PERCENTAGE OF SEVERITY OF PLATEAU RED FACE (PRF)

Region	Severity of PRF			Total	X ² Value	P value
	Mild	Moderate	Severe			
Xining	11 (50%)	8 (36.4%)	3 (13.6%)	22		
Maduo	15 (28.8%)	21 (40.4%)	16 (30.8%)	52	3.8	0.15

TABLE 4. MULTIVARIATE REGRESSION ANALYSIS BETWEEN SEVERITY OF PLATEAU RED FACE AND OTHER INFLUENCE FACTORS

Variable	Unstandardized coefficients		Standardized coefficients	<i>t</i> Value	P Value
	B	Std. Error			
Constant	-0.816	6.029		-0.135	0.892
Age	-0.033	0.006	-0.310	-5.842	0.000
High	-0.017	0.035	-0.139	-0.490	0.625
Weight	0.023	0.051	0.231	0.454	0.650
BMI	-0.082	0.138	-0.249	-0.593	0.554
Hb	0.045	0.023	0.116	1.976	0.050
HR	-0.001	0.004	-0.008	-0.155	0.877
Sao ₂	0.024	0.017	0.082	1.356	0.177
VEGF	0.006	0.001	0.642	10.320	0.000
VC	0.032	0.077	0.021	0.409	0.684
FEV ₁ %	0.016	0.011	0.083	1.489	0.139
FEF _{25%-75%}	-0.197	0.093	-0.118	-2.128	0.035
MVV	0.003	0.003	0.062	1.067	0.288

demonstrated an area under the curve of 0.813 (95% CI=0.753–0.871; $p<0.0001$) for VEGF, 0.679 (95% CI=0.610–0.747; $p<0.0001$) for Hb, and 0.373 (95% CI=0.292–0.454; $p=0.001$) for Sao₂. In addition, according to the multivariate regression analysis, VEGF was one of the main factors that influence the severity of PRF. It might be considered a potentially useful parameter for the diagnosis.

FIG. 1. Concentrations of vascular endothelial growth factor (VEGF) in the subjects with or without plateau red face (PRF) at the altitude of 4300 m (Maduo) and 2260 m (Xining). The PRF group showed significantly higher levels of VEGF than did non-PRF group both in Maduo and Xining. The VEGF levels in Maduo were significantly higher than in Xining both the PRF group and non-PRF group. * $p<0.001$ compared with non-PRF at the same altitude, # $p<0.001$ compared with Maduo.

FIG. 2. Concentrations of vascular endothelial growth factor (VEGF) in the Tibetan and Han Chinese at the altitude of 4300 m (Maduo) and 2260 m (Xining). The VEGF levels in Maduo were significantly higher than in Xining in both Tibetan group and Han group. The Han group showed significantly higher levels of VEGF than Tibetan group in Maduo, whereas no significant difference in Xining. * $p<0.05$ compared with Tibetan group, # $p<0.001$ compared with Maduo.

FIG. 3. Concentrations of vascular endothelial growth factor (VEGF) in males and females at the altitude of 4300 m (Maduo) and 2260 m (Xining). The VEGF levels in Maduo were significantly higher than in Xining, both in males and females, but there were no significant differences between males and females in either Maduo or Xining. # $p<0.001$ compared with Maduo.

FIG. 4. Correlation of Hb (A) and Sao₂ (B) to VEGF in Xining residents. A direct positive correlation was seen between VEGF and Hb, and Sao₂.

Discussion

The new findings of this study are that people living at high altitude may form a unique redness (telangiectasia) of the face, including the cheeks, ear edges, bridge of the nose, and conjunctivae, and those subjects with this ruddy facial color have significantly elevated VEGF levels that are proportionate to the severity of the red facial color. Our data suggest that a number of complex environmental stresses experienced at high altitudes, such as hypoxia, cold weather, and strong ultraviolet light, may lead to higher circulating concentrations of this important angiogenesis compound, which appears to induce the formation of abnormal, new blood vessels of the skin and mucosa, causing the red face and cheeks seen in some people living at high altitudes.

There are two major kinds of environmental stresses at high altitude for humans (Hultgren, 1997). First, there are the alternating daily extremes of climate that often range from hot

sun during the day to freezing nights. In addition, winds are often strong and humidity low, resulting in rapid dehydration. Second, the air pressure is low, which makes it more difficult for oxygen to enter the body, resulting in hypoxia. The climate of Maduo, when compared with Xining, is characterized not only by a lower air pressure (barometric pressure 440 mmHg), but also by a number of complex and interlinked environmental stressors (Ge et al., 1998). The mean annual ambient temperature is 0.2–2.5°C, with a minimal temperature of –35°C. We have frequently observed during physical examination that high altitude residents, particularly subjects with excessive polycythemia, exhibit the ruddy or erythemic facial color, which is called PRF in the Qinghai Plateau, China, and is more common in females (Fig. 7).

This ruddy color most commonly appears in the face and cheeks, but can also extend over the bridge of the nose, around the mouth, and to the conjunctivae. Most PRF subjects, especially Tibetan natives, are asymptomatic, making it

FIG. 5. Correlation of Hb (A) and Sao₂ (B) to VEGF in Maduo residents. A direct positive correlation was seen between VEGF and Hb, while a negative correlation existed with Sao₂.

FIG. 6. Receiver operator characteristic curves (depicting the balance of sensitivity and specificity) for VEGF, SaO_2 , and Hb to diagnose PRF.

unlikely to be a sign of maladaptation to high altitude. On the contrary, it seems to be a positive adaptive response because the ruddiness is primarily due to increased blood flow near the skin surface, providing more oxygen to body tissues. In the present study, we found PRF in 32.9% of subjects living at an altitude of 4300m and 15.7% of subjects at 2260m, suggesting that the occurrence of PRF is closely related to the severity of hypoxic environmental stresses.

High altitude environmental stressors, particularly hypoxia, may lead to a decrease in SaO_2 and rise in hemoglobin concentration. The mean SaO_2 in the Maduo group was 10% lower than the Xining group, and Hb levels were 2.5 g/dL higher. We also found that subjects with PRF in Maduo had lower SaO_2 and higher Hb levels when compared with non-PRF subjects, but these values showed no significant differences between the two groups in Xining. The pathogenesis of

PRF is not clear and it could involve multiple factors. It is generally believed that exposure to extreme environmental stresses, such as hypoxia, cold weather, and strong ultraviolet light can lead to increased blood flow near the skin surface due to dilation of blood capillaries (Penaloza and Arias-Stella 2007; Ge et al. 2011).

VEGF is a 45-kD homodimeric glycoprotein stimulating normal and abnormal vessel growth, and is essential for neoangiogenesis during embryonic development, wound healing, and tumor growth (Okada et al., 2014). Expression of the VEGF gene is mainly stimulated by hypoxia through mediation of hypoxia-inducible factors (HIF), and is up-regulated in vascular smooth muscle cells and endothelial cells under hypoxic conditions (Hubbell et al., 2012; Adeoye et al., 2013; Pichon et al., 2013). Studies (Walter et al., 2001; Hanaoka et al., 2003; Dorward et al., 2007) have shown that circulating VEGF levels may significantly increase when sea level residents acutely ascend to a high altitude, and overproduction of VEGF in the lung attenuates the development of hypoxic pulmonary hypertension due to the protection of an endothelium-dependent function (Partovian et al., 2000; Louzier et al., 2003; Wu et al., 2013).

We also reported previously that significant elevated serum VEGF has been shown in patients with chronic mountain sickness. In the present study, we found that mean levels of serum VEGF in the Maduo group (313.24 pg/mL) was significantly higher than that of the Xining group (152.75 pg/mL; $p < 0.001$). Furthermore, the PRF groups both in Maduo and Xining had significantly higher levels of VEGF than those of non-PRF groups (Fig.1), which have associated lower levels of SaO_2 in PRF groups both in the two altitude regions. In addition, the mean levels of serum VEGF whether in ethnic groups (Fig. 2) or gender groups (Fig. 3) were significantly higher in Maduo than in Xining. And the elevation of VEGF levels in the present study was highly positively correlated with the severity of redness of the face ($r = 0.578$, $p < 0.002$), suggesting that elevations in VEGF may be independently associated with formation of PRF. The area under the curve of ROC for VEGF (0.813) is significantly higher when compared with Hb and SaO_2 , which might be considered a potentially useful parameter for the diagnosis and, perhaps more importantly, prognostic evaluation of PRF.

FIG. 7. A 33-year-old Tibetan woman who has permanently lived at 4300 m, her face was erythemic colored, called “plateau red face.” Hemoglobin was 23 g/dL and VEGF was 530 pg/mL, with telangiectasia of the cheeks.

The pathophysiological consequences of increased VEGF production at high altitudes might contribute to new vessel formation, along with remodeling of pulmonary vessels, proliferation of vascular smooth muscle cells, and consequent loss of distal functional arteries; each of these changes is a potential contributor to the development of PRF. Regardless, how to cure PRF is difficult to answer. The cause of PRF appears to be increased blood circulation due to neoangiogenesis due to high-altitude environmental stressors, and there is no useful method of eliminating or ameliorating this at the present time. But from our study, we clearly recognized that the residents at high altitude could prevent or alleviate the incidence of the PRF by reduced sunlight exposure, greater use of face coverings, and change in altitude. Future studies should concern the multifactors, except high-altitude environment, which influence the incidence of PRF. How to prevent or reduce the incidence of PRF will also be key points in the study of the PRF, with experiments that intervene or perturb the proposed mechanisms, such as pharmacological interventions.

Conclusions

People living at an altitude of 4300 m on the Qinghai Plateau, China, have a higher proportion of red face and cheeks (PRF) than people living at lower altitudes. Those subjects with ruddy facial color have significantly higher levels of serum VEGF when compared to subjects without PRF. The elevation of VEGF was highly positively correlated with the severity of PRF. The mechanism that produces the PRF is not known; however, the environmental stresses of extreme high altitude, such as hypoxia and strong ultraviolet light may stimulate overexpression of VEGF, which perhaps can serve as a marker of PRF.

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Author Disclosure Statement

No conflicting financial interests exist.

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