·临床研究·

以双侧视乳头水肿为主要表现的高原红细胞增多症临床分析

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【摘要】 **目的** 总结以双侧视乳头水肿为主要表现的高原红细胞增多症的临床特点、治疗和预后。**方法** 回顾分析2007年3月至2017年9月共7例以双侧视乳头水肿为主要表现的高原红细胞增多症患者的临床表现、实验室检查、眼科检查、头部影像学检查、线粒体基因检测以及治疗与转归。**结果** 7例患者中男性6例、女性1例，平均年龄为(44.43±9.05)岁，高原居住时间为7(4，13)个月，病程为(28.43±10.05)d，发病初期血红蛋白均>210 g/L；均伴不同程度双侧视乳头水肿，视力为1只眼眼前1 m指数、13只眼矫正视力>0.10，视野缺损类型为2只眼生理盲点扩大、4只眼水平下方视野缺损、2只眼中心暗点、6只眼弥漫性视野缺损；7例头部MRI可见额顶叶或侧脑室旁点片状长T_1、长T_2异常信号影；7只眼视神经MRI可见视神经信号增高，呈轻度强化；均予抗血小板和改善微循环治疗，随访6个月视力恢复良好。**结论** 以双侧视乳头水肿为主要表现的高原红细胞增多症易误诊为其他疾病。脱离高原环境、降低血红蛋白含量、辅以抗血小板和改善微循环治疗可以促进视力恢复。

【关键词】 红细胞增多症； 视乳头水肿； 高海拔

Clinical analysis of high altitude polycythemia manifested as bilateral papilledema

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【**Abstract**】 **Objective** To investigate the clinical features, treatment and prognosis of high altitude polycythemia mainly manifested as bilateral papilledema. **Methods** Clinical data of 7 patients with high altitude polycythemia mainly manifested as bilateral papilledema in our hospital from March 2007 to September 2017 were retrospectively analyzed, including clinical manifestations, laboratory results, ophthalmologic examinations, head imaging features, mitochondrial gene detection, treatment and prognosis. **Results** There were 6 male patients and one female patient, with mean age (44.43 ± 9.05) years old, high altitude residence 7 (4, 13) months, and duration (28.43 ± 10.05) d. All patients were detected with high concentrations of hemoglobin (> 210 g/L), and different degrees of bilateral papilledema after onset. One eye had severe vision impairment [best corrected visual acuity (CVA) was finger counting], and the CVA of other 13 eyes were > 0.10. Visual field defects included enlargement of psychological blind spot (2 eyes), lower altitudinal visual field defect (4 eyes), central scotoma (2 eyes) and diffuse visual field defect (6 eyes). Brain MRI of 7 cases showed dot-like and patchy long T_1 and long T_2 signals in frontal lobe, parietal lobe and paraventricular region. Optic nerve MRI showed hyperintense signal and slight enhancement in 7 eyes and no abnormality in other 7 eyes. All patients were treated by antiplatelet therapy and microcirculation improvement. Best CVA of all patients were remarkably improved within follow up of 6 months. **Conclusions** High altitude polycythemia mainly manifested as bilateral papilledema was easily misdiagnosed as other diseases. Moving away from plateau, decreasing hemoglobin, anti-platelet therapy and microcirculation improvement may play an important role in the favorable prognosis.

【**Key words**】 Polycythemia; Papilledema; Altitude

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高原红细胞增多症(HAPC)系高原低氧引起的以红细胞过度代偿性增生为主的临床综合征。2004年第六届国际高原医学大会制定的高原红细胞增多症诊断标准:长期居住在海拔>2500 m地方,男性血红蛋白(Hb)≥210 g/L、女性≥190 g/L[1]。由于红细胞异常增多,血液黏滞度增加,微循环障碍,导致全身各组织器官广泛性损害,引起头晕、头痛、气促等一系列临床症状,严重者甚至可因血管栓塞而猝死[2-3]。本研究回顾分析近10年首都医科大学附属北京同仁医院诊断与治疗的7例以双侧视乳头水肿为主要表现的高原红细胞增多症患者的临床资料,以期提高疾病的诊断与治疗水平。

临床资料

一、病例选择

1. 纳入与排除标准 (1)高原红细胞增多症的诊断均符合2004年第六届国际高原医学大会制定的标准[1]。(2)排除慢性肺病或慢性呼吸紊乱,或者某些慢性病引起的低氧血症等导致的继发性红细胞增多症,如肺气肿、支气管炎、支气管扩张、肺泡纤维变性、肺癌等;其他眼科疾病。

2. 一般资料 选择2007年3月至2017年9月在首都医科大学附属北京同仁医院神经内科住院治疗的高原红细胞增多症患者共7例,均为汉族,男性6例,女性1例;发病年龄34~56岁,平均(44.43±9.05)岁;移居高原(海拔>3000 m)时间3~22个月,中位时间7(4,13)个月;发病至明确诊断时间20~50 d,平均(28.43±10.05)d。

二、临床表现

1. 临床症状与体征 7例患者均呈急性发病,发病视力下降即达高峰,发病前均有不同程度头痛、头晕、乏力史;临床表现为视力下降或视物遮挡,伴眼部不适感或轻微胀痛,1例(1/7)为单眼起病、6例(6/7)为双眼同时或相继起病(表1)。

2. 血清学和脑脊液检查 (1)血清学:7例患者入院时血红蛋白均>210 g/L(男性120~160 g/L,女性110~150 g/L),血清抗水通道蛋白4(AQP4)抗体和免疫学指标均于正常值范围(表1)。(2)脑脊液:本组7例患者腰椎穿刺脑脊液检查压力、常规和IgG合成率均于正常值范围;2例(例1、例2)蛋白定量轻度升高,均为460 mg/L(150~450 mg/L),5例生化指标于正常值范围(表1)。

3. 眼科检查 7例患者(14只眼)均行眼科检查,包括视力、静态视野(Humphrey视野)、眼底镜、光学相干断层扫描术(OCT)和视神经MRI。1只眼(例3)视力为眼前1 m指数,余13只眼矫正视力均≥0.10。视野缺损类型为生理盲点扩大(2只眼),水平下方视野缺损(4只眼),中心暗点(2只眼),弥漫性视野缺损(6只眼)。眼底镜和OCT显示,14只眼不同程度视乳头水肿,血管模糊不清,伴或不伴视盘周围出血(表1)。视神经MRI检查7只眼可见视乳头、视神经眶内段或球内段高信号影,增强扫描呈强化征象(图1),7只眼无明显异常,其中,病程较长患者可见视神经变细。

4. 头部影像学检查 7例患者均进行MRI检查,7例头部MRI可见额顶叶或侧脑室旁点片状长T_1、长T_2异常信号影(图2)。7例患者均行颈动脉超声和经颅多普勒超声(TCD),2例(例1、例5)存在颈动脉内膜增厚,5例正常(表1)。

5. 线粒体基因检测 7例患者均于入院时抽取外周静脉血3 ml,送检首都医科大学附属北京同仁医院中心实验室,采用Singer法行线粒体基因检测,均呈阴性(表1)。

三、诊断、治疗与转归

本组7例患者最终明确诊断为高原红细胞增多症,其中有3例(例2、例4、例5)在当地医院诊断为"视神经炎",2例(例2、例5)予甲泼尼龙1000 mg/d(×3 d)静脉滴注冲击治疗后序贯1 mg/(kg·d)口服;1例(例4)予甲泼尼龙48 mg/d口服,2周后序贯减量,即24 mg/d(×7 d)、12 mg/d(×7 d),逐渐减停。明确诊断后均予阿司匹林100 mg/d口服抗血小板和羟苯磺酸钙0.50 g/次、3次/d口服改善微循环治疗。本组患者住院9~13 d,平均(11.14±1.35)d;出院后随访6个月,视力均恢复良好。

讨 论

高原红细胞增多症的发病机制较为复杂,目前尚未完全阐明。通常认为,红细胞生成平衡是生理造血的特点,任何原因引起的成熟红细胞与未成熟红细胞之间、红细胞生成与死亡之间平衡失调,均有可能导致病理造血状态[4]。由于红细胞异常增多,血液黏滞度显著增加,微循环障碍,导致全身多脏器、多系统不同程度损害[5]。

目前认为,促红细胞生成素(EPO)水平升高是红细胞增多的主要原因[6]。促红细胞生成素的效应细胞主要包含从红细胞系造血祖细胞到早幼红细

表1 7例高原红细胞增多症患者的临床资料

Table 1. Clinical data of 7 patients with high altitude polycythemia

Case	Sex	Age (year)	High altitude residence (month)	Duration (d)	Involved eye	Serum		CSF			Visual acuity (OD/OS)	Visual field (OD/OS)	Disc edema	Optic nerve MRI	Brain MRI	Carotid ultrasound	Detection of mitochondrial gene mutation
						Hb (g/L)	Anti-AQP4 and immunological indexes	Pressure (mm H_2O)	WBC ($\times 10^6$/L)	Biochemical detection							
1	Male	52	4	25	Both (simultaneously)	213	–	90	0	Protein 460 mg/L, glucose and chloride normal	0.60/1.00	Diffuse field defect/ enlargement of blind spot	Both	Coronal T_2WI fat suppression showed high signal in the anterior segment of the optic nerve. Axial enhanced T_1WI showed mild enhancement in the orbital and bulbar segments of the optic nerve	Axial T_2WI showed dot-like high signal mainly distributed in bilateral frontal, parietal lobes	Carotid intima thickening	–
2	Male	34	13	30	Both (simultaneously)	223	–	150	0	Protein 460 mg/L, glucose and chloride normal	0.60/0.30	Enlargement of blind spot/ diffuse field defect	Both	Coronal T_2WI fat suppression showed the orbital segment of the optic nerve was slightly thinner and high signal. Axial enhanced T_1WI showed the marginal of the left optic nerve was slightly enhanced	Axial T_2WI showed dot-like high signal adjacent to lateral ventricle	Normal	–
3	Male	36	22	25	Right	236	–	180	0	Protein 200 mg/L, glucose and chloride normal	1 m figure counting/ 1.00	Diffuse field defect/lower altitudinal visual field impairment	Both	Coronal T_2WI fat suppression showed high signal in the the right optic nerve. The left optic nerve was normal	Axial T_2WI showed dot-like and patchy high signal adjacent to lateral ventricle	Normal	–
4	Male	53	3	50	Both (successively)	214	–	160	2	Protein 380 mg/L, glucose and chloride normal	1.00/0.12	Lower altitudinal visual field impairment of two eyes	Both	Both optic nerves were normal	Axial T_2WI showed dot-like high signal mainly distributed in bilateral frontal lobes and left lateral ventricle	Normal	–
5	Female	56	5	20	Both (simultaneously)	221	–	135	0	Protein 370 mg/L, glucose and chloride normal	0.70/0.90	Diffuse field defect of two eyes	Both	Both optic nerves were normal	Axial T_2WI showed dot-like high signal mainly distributed in frontal, parietal lobe	Carotid intima thickening	–
6	Male	42	13	22	Both (simultaneously)	230	–	125	0	Protein 290 mg/L, glucose and chloride normal	0.50/0.80	Diffuse field defect/central scotoma	Both	Axial enhanced T_1WI showed the optic papilla was slightly enhanced. The right was normal	Axial T_2WI showed dot-like and patchy high signal mainly distributed in frontal, parietal lobe and lateral ventricle	Normal	–
7	Male	38	7	27	Both (simultaneously)	216	–	140	1	Protein 330 mg/L, glucose and chloride normal	0.10/0.90	Central scotoma/ lower altitudinal visual field impairment	Both	Axial enhanced T_1WI showed the left optic nerve was slightly enhanced. The right was normal	Axial T_2WI showed dot-like high signal mainly distributed in right parietal lobe	Normal	–

–, negative, 阴性。Hb, hemoglobin, 血红蛋白; AQP4, aquaporin 4, 水通道蛋白4; CSF, cerebrospinal fluid, 脑脊液; WBC, white blood cell, 白细胞计数; OD, oculus dexter, 右眼; OS, oculus sinister, 左眼

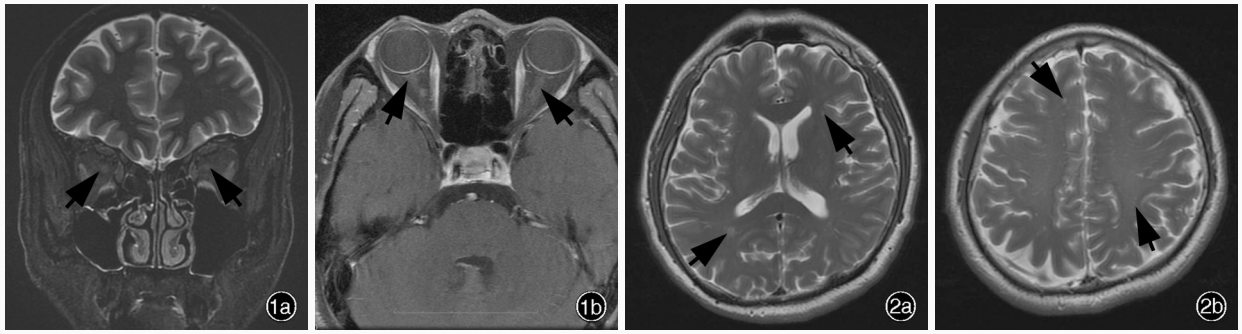

图1 例1患者，男性，52岁，临床诊断为高原红细胞增多症。视神经MRI检查所见 1a 冠状位短时间反转恢复（STIR）序列显示，双侧视神经前段信号增高（箭头所示） 1b 横断面增强T_1WI显示，视神经眶内段和球内段轻度强化征象（箭头所示） **图2** 例6患者，男性，42岁，临床诊断为高原红细胞增多症。头部MRI检查所见 2a 横断面T_2WI显示，侧脑室旁片状异常高信号影（箭头所示） 2b 横断面T_2WI显示，额顶叶点状异常高信号影（箭头所示）

Figure 1 A 52-year-old male (Case 1) was clinically diagnosed as high altitude polycythemia. MRI findings of optic nerve Coronal short-tau inversion recovery (STIR) showed high signal in anterior segments of bilateral optic nerves (arrows indicate, Panel 1a). Axial enhanced T_1WI showed mild enhancement in the orbital and bulbar segments of optic nerve (arrows indicate, Panel 1b). **Figure 2** A 42-year-old male (Case 6) was clinically diagnosed as high altitude polycythemia. Brain MRI findings Axial T_2WI showed patchy high signal adjacent to lateral ventricle (arrows indicate, Panel 2a). Axial T_2WI showed dot-like high signal mainly distributed in frontal and parietal lobes (arrows indicate, Panel 2b).

胞等的一系列红细胞发生细胞，并加速血红蛋白的合成和骨髓中网织红细胞的释放。本组男性患者占绝大多数（6/7例），与文献报道相似[7]，可能因为睾酮分泌异常和促红细胞生成素水平升高均可以引起高原红细胞增多症。业已证实，睾酮有抑制肺通气并促进红细胞生成的作用[8]。国内张朝霞等[9]的调查数据显示，青海省海西地区男性高原红细胞增多症患病率为6.14%，女性为1.03%。高原红细胞增多症的发病具有明显种族和地域差异，欧洲人群较安第斯山脉世代居住人群更易患病，世代居住在高原地区的藏族人群发病率（1.21%）显著低于世代居住在相同海拔高度的安第斯山脉人群（15%）和移居高原的汉族人群（5.59%）[10-11]。

国内外文献罕见以视乳头水肿为主要表现的高原红细胞增多症病例。徐哲等[12]对215例高原红细胞增多症患者进行眼科检查，15例（6.98%）发生视乳头水肿，210例正常对照者中仅2例（0.95%）发生视乳头水肿；进一步亚组分析显示，高原红细胞增多症患者眼部表现与疾病严重程度密切相关：患者居住高原时间长达5年以上，眼部表现多伴结膜血管改变、视网膜血管改变和视网膜出血渗出。本研究7例患者移居高原的时间相对较短，结膜和视网膜血管的慢性病理生理改变尚未形成，眼科检查仅可见视乳头水肿，未见其他眼部改变。这也导致部分患者首次就诊时误诊为其他疾病，如视神经炎和颅内压增高等。

高原红细胞增多症呈急性发病，类似脑卒中样发作。有文献报道，缺血性卒中是临床最常见的红细胞增多症诱发的脑血管病变，这是因红细胞异常增多造成的高凝状态可导致脑组织供血障碍[12-13]；视神经的血液供应和解剖学结构与脑组织相似，故与睫状后动脉缺血可能存在密切联系[14]，因此，二者发病形式相似。部分患者表现为类似前部缺血性视神经病变的视野缺损特点。本研究视神经MRI显示，发病时间较长、症状较轻微的患者视乳头未见强化，而发病时间较短、视力损害严重的患者可见视乳头和视神经前段不同程度强化；头部MRI显示皮质下和侧脑室旁点片状梗死灶，提示可能累及脑小血管并出现相应改变，究其原因，可能与慢性脑组织缺氧缺血导致小血管壁发生病理生理改变有关[13]。

双侧视乳头水肿在神经科的最常见疾病是颅内压增高综合征。本组有1例患者（例1）入院时双侧视乳头水肿较严重，曾高度怀疑颅内压增高综合征。颅内压的变化取决于3项因素，即脑组织、脑脊液和脑血流量（CBF）。因此从理论上讲，高原红细胞增多症不会出现颅内压增高，本组患者脑脊液压力均正常亦证实这一推论，且头部MRI亦未见颅内压增高的间接征象，例如蛛网膜下隙增宽、空蝶鞍等[15-16]，而脑脊液常规、病原学和免疫学指标均正常，蛋白定量仅轻度升高，更加证实视乳头水肿与血液高凝状态导致视盘微循环障碍有关。

本组有3例患者首诊于当地医院诊断为视神经炎，予甲泼尼龙冲击和序贯治疗，未见明显效果。由此可见，高原红细胞增多症以视力下降、视乳头水肿为主要表现时，易与视神经炎和遗传性视神经病变相混淆。除详细询问病史外，血清抗AQP4抗体和线粒体基因检测具有重要意义。

与其他引起视力下降的常见视神经病变不同，本组患者视功能障碍相对较轻，主要表现为不同程度和类型的视野缺损，无明显色觉改变。究其原因，此类患者损害的是视乳头，视乳头病变造成的视功能障碍通常较轻微，而视力下降是视功能障碍的最终表现。大多数视乳头水肿是可逆的，早期积极治疗易恢复[17]。在本研究中，患者脱离高原环境后，血红蛋白含量呈现逐步下降趋势，同时予抗血小板和改善微循环治疗，视乳头水肿减轻，视力恢复良好。

综上所述，以视乳头水肿为主要表现的高原红细胞增多症患者由于不具有其他神经功能缺损症状，临床易误诊和漏诊。提示临床医师应提高对不明原因视乳头水肿的重视，尽可能详细采集病史，重视每项异常的实验室指标，早期测量颅内压，对明确诊断具有重要意义。因此，早期积极降低血红蛋白含量，不仅是挽救视力的最重要方法，而且可以避免临床更多其他重要脏器栓塞事件的发生。

利益冲突 无

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