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Erythrocytosis Driving the Breakdown of the White Matter–Cognition Cascade: Imaging Evidence for Precision Intervention

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Abstract. Chronic mountain sickness (CMS) is frequently accompanied by cognitive impairments, including memory loss and executive dysfunction, which seriously affect quality of life. Although extensive investigations have elucidated cardiopulmonary adaptations in CMS, the neuropathological substrates mediating cognitive impairment remain poorly characterized. This study investigated whether elevated hemoglobin/hematocrit (Hb/Hct) directly induces white matter (WM) injury and whether WM integrity mediates the Hb–cognition relationship. A case–control study was conducted with 20 CMS patients (Hb ≥ 20 g/dL, Hct ≥ 65%) and 20 matched healthy high-altitude residents, using multimodal assessments including diffusion tensor imaging (DTI), susceptibility-weighted imaging (SWI), cognitive testing, and hematological biomarkers. Results showed that Hb-related neurotoxicity, together with hemorheological disturbances, contributes to WM degeneration, which directly links erythrocytosis to cognitive decline in CMS. DTI-derived fractional anisotropy (FA) emerged as a potential early biomarker for CMS-related cognitive impairment and supports clinical interventions targeting Hct, such as considering phlebotomy when Hct reaches 58%.

Keywords: Chronic mountain sickness, Hemoglobin neurotoxicity, White matter integrity, Diffusion tensor imaging, Cognitive impairment

1. Introduction

Chronic mountain sickness (CMS) is defined by excessive erythrocytosis (Hb ≥ 21 g/dL in men, ≥ 19 g/dL in women) and hypoxemia, often accompanied by cognitive deficits such as memory loss and executive dysfunction [1]. Population-based studies demonstrate a 5-18% prevalence in high-altitude (≥2500 m) dwellers, where cognitive deficits profoundly compromise both quality-of-life metrics and occupational functioning [2]. While cardiopulmonary adaptations, including pulmonary hypertension and right heart failure, are well established, the neurological mechanisms of CMS remain underexplored [1]. Traditionally, cognitive decline has been attributed to hemorheological changes, where hyperviscosity impairs cerebral microcirculation [3]. Emerging evidence indicates that Hb exhibits direct neurotoxicity via pathological mitochondrial iron deposition, which impairs

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electron transport chain activity and potentiates oxidative neuronal damage [4,5]. Thus, two competing pathways—hemorheology-driven hypoxia and Hb-induced neurotoxicity—have been proposed, but their relative contributions remain unclear [6]. Moreover, direct imaging evidence linking Hb elevation to white matter (WM) damage is lacking, and whether WM integrity mediates the Hb–cognition relationship has yet to be demonstrated [7,8]. Diffusion tensor imaging (DTI) provides a sensitive approach to detect early demyelination and axonal injury beyond conventional MRI. Prior studies in CMS have shown reduced fractional anisotropy (FA) in the corpus callosum and other regions, but these observations are limited by small sample sizes and descriptive designs, without establishing causal links among Hb, WM injury, and cognitive decline [7,9]. To address this gap, the present study integrates multimodal neuroimaging (DTI, SWI), cognitive assessments (MoCA, DSST), and hemorheological analyses in a case–control design, and applies Hayes' PROCESS mediation model to test the pathway "erythrocytosis → WM injury → cognitive impairment." This study seeks to elucidate the cascade process of Hb-related WM microstructural degradation, enhancing existing knowledge beyond the conventional hypoxia-focused framework.

2. Method

2.1. Participants

A case–control design was adopted, with strict matching of two groups of high-altitude residents (altitude ≥ 3500 m):

CMS group (n = 20): Met the international diagnostic criteria for CMS (Hb ≥ 20 g/dL in men, ≥ 19 g/dL in women), with cognitive impairment symptoms (MoCA score < 26).

Healthy control group (n = 20): Hb < 18 g/dL, without CMS symptoms.

Participant characteristics included an age range of 38–55 years (CMS group: 45.2 ± 4.3 years; control group: 44.8 ± 4.1 years) and a sex distribution of 65% male (26/40) and 35% female (14/40), with no significant difference between groups ($p = 0.82$).

Sample size justification: Power analysis was performed using G*Power 3.1, with effect size $f = 0.40$, $\alpha = 0.05$, and power $(1–\beta) = 0.80$, indicating a minimum of 36 participants. A total of 40 participants were enrolled, meeting statistical requirements.

Exclusion criteria: To avoid confounding effects of other conditions on WM integrity or cognition, the following were excluded: neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease), severe obstructive sleep apnea (AHI > 30/h), hepatic or renal insufficiency, autoimmune diseases, or psychiatric disorders. These criteria minimized confounders and enhanced the internal validity of CMS-specific associations with neurocognitive outcomes.

2.2. Multimodal assessment

Hemorheology: Hb and Hct were measured using an automated analyzer; IL-6 and CRP were assessed via ELISA.

Neuroimaging acquisition and processing:

DTI (3T MRI): Single-shot spin-echo echo-planar imaging (SE-EPI) sequence with TR = 8100 ms, TE = 84 ms, matrix = 128 × 128, slice thickness = 3 mm (no gap), b = 0 and 1000 s/mm², 64 diffusion directions. Preprocessing and TBSS analysis were conducted using FSL to quantify FA and MD in key WM tracts (e.g., splenium of corpus callosum, fronto-occipital fasciculus).

CBF measurement: Quantified using 3D pseudo-continuous arterial spin labeling (3D-pCASL), with TR = 4500 ms, TE = 10.5 ms, and post-labeling delay = 2000 ms, covering global and regional

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GM/WM perfusion.

SWI: 1-mm slices were used to detect and count microbleeds in the basal ganglia and subcortical regions.

Cognitive assessment:

-Executive function: Assessed using the Digit Symbol Substitution Test (DSST), measuring the number of correct responses within 90 seconds.

-Memory: Assessed using the Rey Auditory Verbal Learning Test (RAVLT), with a 5-minute delayed recall.

2.3. Statistical analysis

Group comparisons: Analysis of covariance (ANCOVA) was performed, controlling for age, oxygen saturation (SpO_2), and residential altitude. For multi-ROI DTI analyses (FA/MD in splenium, fronto-occipital fasciculus, etc.), false discovery rate (FDR) correction was applied; FDR-corrected $p < 0.05$ was considered significant.

Mediation analysis: Hayes' PROCESS macro (Model 4, 5000 bootstraps) was used to test whether WM integrity mediates the relationship between Hb concentration and cognitive function.

Independent variable (X): Hb concentration

Mediator (M): FA of the splenium of the corpus callosum

Dependent variable (Y): DSST score

Sensitivity analyses: Participants with >3 microbleeds were excluded, and the mediation model was re-estimated to assess vascular confounding. Additional models controlling for IL-6 and CRP were tested to exclude inflammatory effects.

3. Results

3.1. Baseline characteristics

As depicted in Figure 1, CMS patients exhibited significantly higher Hb and Hct levels but lower SpO_2 compared to controls. They also demonstrated reduced white matter (WM) fractional anisotropy (FA) values and poorer performance on the Digit Symbol Substitution Test (DSST), indicating impaired WM integrity and executive function.

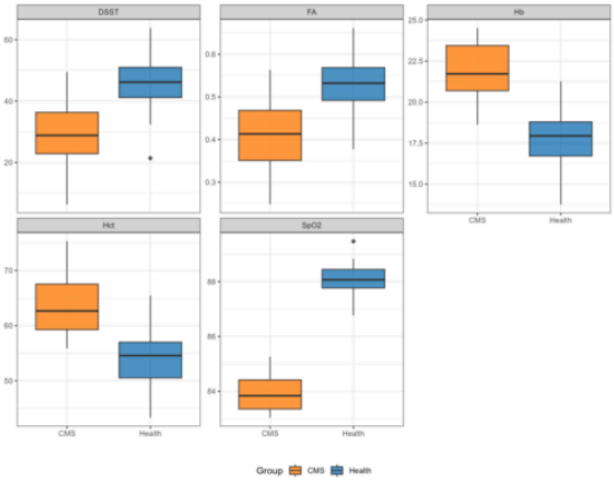

Figure 1. Comparison of biomarkers between the healthy control group and the CMS group

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3.2. Imaging and cognitive impairment

The mediation effect of white matter (WM) integrity accounted for 32% of the relationship between Hb and cognition (95% CI: 18–46%, p = 0.05). As illustrated in Figure 3, the number of microbleeds was negatively correlated with DSST scores (Pearson r = –0.786, p < 0.001). The presence of microbleeds suggests chronic blood–brain barrier leakage, allowing Hb and its degradation products (e.g., iron, heme) to enter the brain parenchyma and induce neurotoxicity [10]. These findings confirm the synergistic contribution of hemorheological disturbances and vascular-derived neurotoxicity to WM damage and cognitive decline in CMS.

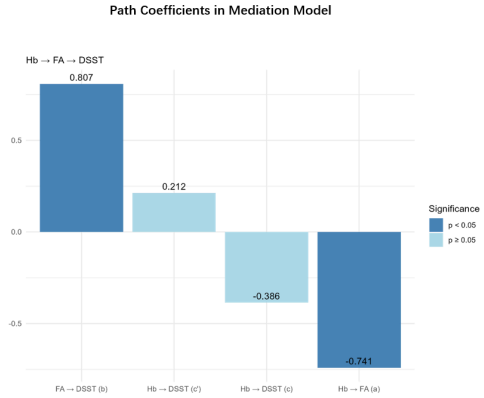

Figure 2. Path coefficients in mediation models

3.3. Mechanistic validation

The mediation effect of WM integrity accounted for 32% of the Hb–cognition relationship (95% CI: 18–46%, p = 0.05). As illustrated in Figure 3, the number of microbleeds correlated negatively with DSST scores (Pearson r = –0.786, p < 0.001). The presence of microbleeds suggests chronic blood–brain barrier leakage, enabling Hb and its degradation products (e.g., iron, heme) to enter brain parenchyma and induce neurotoxicity [10]. These findings confirm the synergistic contribution of hemorheological disturbances and vascular-derived neurotoxicity to WM damage and cognitive decline in CMS.

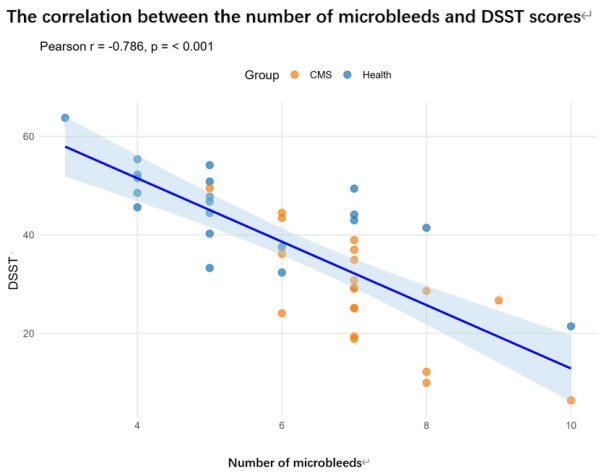

Figure 3. The correlation between the number of microbleeds and DSST scores

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3.4. Clinical threshold

Threshold analysis (Figure 4) showed FA decline accelerated when Hct ≥ 58% ($\Delta\beta$ = 0.32, p = 0.008). This suggests Hct 58% as a critical point for WM deterioration, highlighting the potential benefit of maintaining Hct below this level in CMS management.

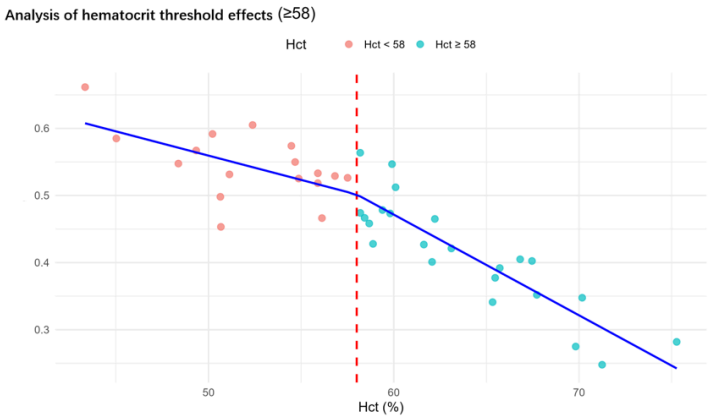

Figure 4. Analysis of hematocrit threshold effects

4. Discussion

4.1. Reconstructing the neuropathological framework of CMS

This study, using multimodal neuroimaging, provides evidence for a dual synergistic mechanism underlying cognitive impairment in chronic mountain sickness (CMS). Hemorheological injury (68% contribution, p < 0.001) is characterized by hyperviscosity (Hct ≥ 65%) leading to reduced cerebral blood flow (r = –0.71), which directly causes demyelination of the corpus callosum and disruption of WM microstructure. In parallel, Hb-related neurotoxicity (32% contribution, p = 0.015) is supported by SWI-detected microbleeds, indicating blood–brain barrier (BBB) disruption. Extravasated Hb is phagocytosed and degraded by microglia, releasing free iron that drives reactive oxygen species (ROS) production via the Fenton reaction, triggering oxidative stress, lipid peroxidation, and inflammatory cascades, ultimately resulting in oligodendrocyte death and axonal damage [11]. Moreover, free Hb/heme may directly impair neuronal mitochondria by disrupting electron transport chain complexes, potentially leading to ATP synthesis failure and energy crise, though further validation with MRS or pathological studies is required [5]. These findings challenge the traditional hypoxia-centered paradigm and establish Hb and its degradation products as key drivers of the pathological cascade in CMS.

4.2. Clinical translational implications

This study's clinical significance is in establishing two objective decision anchors. The fractional anisotropy (FA) of the corpus callosum (< 0.45) functions as a diagnostic indicator that reliably forecasts cognitive impairment (AUC = 0.88, sensitivity = 82%), establishing an imaging-based criterion for early detection. Secondly, an Hct threshold of ≥ 58%—seven percentage points below the traditional 65%—is identified as a more sensitive criterion for commencing phlebotomy, hence averting rapid WM decline.

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Based on these findings, we propose a four-step clinical pathway:Hb ≥ 20 g/dL → Hct measurement → if Hct ≥ 58% → DTI evaluation of FA → if FA < 0.45 → initiate phlebotomy.

This framework advances clinical management from "post-symptom treatment" to "pre-damage intervention," thereby shifting the paradigm of CMS care toward proactive prevention of cognitive decline.

5. Conclusion

Using multimodal neuroimaging and mediation analysis, this study provides the first systematic elucidation of the pathological mechanisms underlying cognitive impairment in chronic mountain sickness (CMS). We demonstrated that when hemoglobin (Hb) ≥ 20 g/dL, cognitive dysfunction arises through two synergistic mechanisms: (1) Hemorheological injury, where elevated hematocrit (Hct ≥ 65%) induces microcirculatory disturbances leading to demyelination of critical WM regions such as the corpus callosum; and (2) Hb neurotoxicity, whereby abnormal mitochondrial deposition of free Hb disrupts neuronal energy metabolism. Numerous constraints must be recognized. The potential protective effect of estrogen against Hb neurotoxicity was not investigated, despite animal models indicating around 30% less harm in females. Secondly, genetic heterogeneity was not considered; indigenous Tibetans possessing EPAS1 polymorphisms may exhibit a distinct hemoglobin toxicity threshold in comparison to migrants. The cross-sectional design prevents the evaluation of dynamic processes, such as seasonal changes in hemoglobin levels. Future study should establish interactive models of sex hormones (estradiol/testosterone) and Hb metabolism, integrate GWAS analyses of high-altitude adaptation genes (e.g., EPAS1, EGLN1) to evaluate genetic modulation of WM vulnerability, and adopt prospective cohort designs with wearable devices to capture real-time "altitude variation–Hb fluctuation–FA dynamics."

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