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CASE REPORT

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A frontotemporal dementia-like case after high-altitude climbing

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Abstract

Background We report a case who developed long-term neuropsychiatric sequelae similar to frontotemporal dementia after suffering a "high altitude sickness" while climbing a high mountain without taking precautions against acute hypoxia.

Case presentation The 57-year-old patient showed symptoms of acute mountain sickness after climbing 3500 m. A few months after descending the mountain, he developed symptoms such as loss of empathy, decreased speech, perseveration, echolalia, and increased interest in sugary foods. The patient's MRI and PET/CT results were consistent with frontotemporal neurodegeneration. After the start of donepezil, persecution delusions developed, and the clinical picture worsened. In the process, he developed visual agnosia and anomic aphasia. Although there was no significant change in personality traits at the beginning, the patient developed apathy, loss of inhibition, lack of empathy, progressive aphasia, and problems perceiving and expressing emotions. A significant loss of function occurred within 4 years. The patient met the criteria for "probable behavioral variant frontotemporal dementia", but was defined as a frontotemporal dementia-like case due to possible relevance to a medical condition affecting the brain.

Conclusions This case suggests that clinicians should be more careful about the chronic consequences of high-altitude diseases and avoid cholinesterase inhibitors such as donepezil, as it can worsen behavioral symptoms of frontotemporal dementia-like symptomatology.

Keywords High altitude sickness, Possible frontotemporal dementia, Neuropsychiatric sequelae, Donepezil, Case report

Background

"High-altitude diseases", a common ailment in mountaineers and mountain hikers, usually manifest themselves with the development of cerebral and pulmonary syndromes in people not acclimatized after climbing above 2500 m [1]. In a study conducted in Colorado in 1991, acute mountain sickness was 22% at altitudes between 1850 and 2750 m and 42% at altitudes of 3000 m and above [2]. The minor form, called "acute mountain sickness", is characterized by headache, insomnia, dizziness, malaise, fatigue, loss of appetite, and nausea or vomiting. Besides the main form of "high-altitude cerebral edema", ataxia, somnolence, dysarthria, diplopia, nystagmus, trunk ataxia, pyramidal symptoms, and loss of consciousness can also be observed [2, 3]. Neurological conditions such as mental disorders, focal neurological deficits, and transient global amnesia are also detected [1].

A drastic decrease in arterial PCO2 due to intense pulmonary gas exchange during rapid climbing to extreme heights can result in rapid vasoconstriction. This mechanism increases hypoxic damage, especially in the small vascular regions of the brain, with increased blood viscosity in a high mountain environment [4]. The incidence

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of high-altitude sickness depends on the climb speed; the altitude reached at which the person sleeps, and individual physiology. Risk factors include a history of high-altitude diseases, residence below 900 m, overexertion, and pre-existing cardiopulmonary diseases [2]. Most studies on this subject have focused on pulmonary edema and cerebral dysfunction in the acute phase of the disease. However, few reports have yet to emerge on the neuropsychiatric sequelae of high-altitude cerebral edema [5].

As with CO poisoning, hypoxia increases the amount of extracellular fluid passing through the vasogenic endothelium in the brain, causing neurons to be unable to maintain their normal transmembrane ionic gradient and homeostasis. A positive feedback loop develops, resulting in neuronal destruction induced by excitotoxicity, oxidative and nitrative stress, neuroinflammation, and apoptosis. Cholinergic, gamma-aminobutyric acid (GABA), beta-adrenergic and serotonergic systems are altered, and neurotransmission functioning is impaired, especially in the neocortex and hippocampus [6]. After a few days of acute neuroinflammation, subacute neuroinflammation lasting 2–6 weeks continues, with post-ischemic inflammation lasting for months or years. Late post-ischemic neuroinflammation leads to secondary damage of neuronal cells. After the sequence of events begins, the neuroinflammation process may become overactive, causing further cellular damage and loss of neuronal function [7]. This may result in the development of neurodegenerative diseases.

In this case report, we presented a 57-year-old male who developed acute mountain sickness symptoms after climbing Mount Everest to 3500 m in Nepal and subsequently developed frontotemporal neurodegeneration.

Case presentation

The patient is a 57-year-old male, a university graduate, and a successful architect. He is divorced from his wife and has two children. He lives with his fiancée. The patient continued to work in his office and could do his job until a year ago.

The patient was brought to our clinic by his fiancée because of the complaints that he lived in fear, kept the curtains closed all the time, said that the gendarme would take him away, and could not sleep.

His complaints started 4 years ago after climbing 5416 m in Nepal. The patient, experiencing nausea, vomiting, headache, malaise, and fatigue at the 3500th meter of the climb without oxygen support, recovered within 12 h after a rapid descent of 400 m, and continued climbing afterward. The patient, who has been climbing at an amateur level for 10 years, had climbed to a maximum height of 750 m before this climb. The patient, residing at sea level, climbed to 5416 m in 19 days and slept at a maximum altitude of 3500 m. A few months after returning from Nepal, he started to decrease his speech, repeating the same things repeatedly, having difficulty expressing his feelings, and losing empathy. He reacted to a sad event with a smile and did not care about the problems in his life. During this period, there was also an increase in sexual desire and appetite. He especially prefers sweet foods.

He was diagnosed with dementia, and donepezil was started 1 year ago. A few months later, the patient started to have psychotic symptoms. The patient was referred to us when persecutory delusions began.

No history of head trauma, alcohol and substance use, exposure to toxins, and any psychiatric disorder or medical illness was detected in the patient except for hypertension. However, in the patient's family history, his paternal grandmother was found to be diagnosed with Alzheimer's disease.

No pathological finding was detected in his physical examination. Visual agnosia and anomic aphasia were revealed during his neurological examination. There was no impairment in reading and writing.

In his mental status examination in the third year of the disease, the patient was conscious, fully oriented, and cooperative. Speech rate and quantity decreased. His associations got slower, and his thought content was poor. There were also perseverations in the patient's speech. His spontaneous attention was impaired, and his affect was inappropriate. He had persecutory delusions.

No pathological finding was detected except for high-level triglyceride (531 mg/dl) and cholesterol (VLDL: 106.2 mg/dl). RBC, HGB, and HCT were at the lower limit. IUBC: 112 µg/dl, total Fe binding capacity: 215 µg/dl (low). Thyroid function tests, urinalysis, vitamin B12, and folic acid values were within normal limits. Hepatitis markers (HBsAg and Anti HCV negative), anti-HIV, and serological tests (VDRL/RPR) were negative. Electroencephalogram (EEG) was reported as normal. In MRI findings, cerebral sulci on the left side of the frontotemporal region were asymmetrically deeper than those on the right. There was also dilatation in the lateral ventricles. Besides, millimetric-sized nonspecific gliotic lesions were identified in the white matter of the cerebral hemisphere (Fig. 1). In PET/CT, hypometabolism was detected in the bilateral frontotemporal region. In genetic analysis, normal allele E3/E3 was detected due to Apolipoprotein E (ApoE) (E2, E3, E4) mutation screening.

While the patient completed the A form of the trail-making test in 62 s without error, he could not complete the B form. The patient's maintenance of the set was severely slowed down. The set-shifting skill was observed to be complete in Luria's drawing test. In the

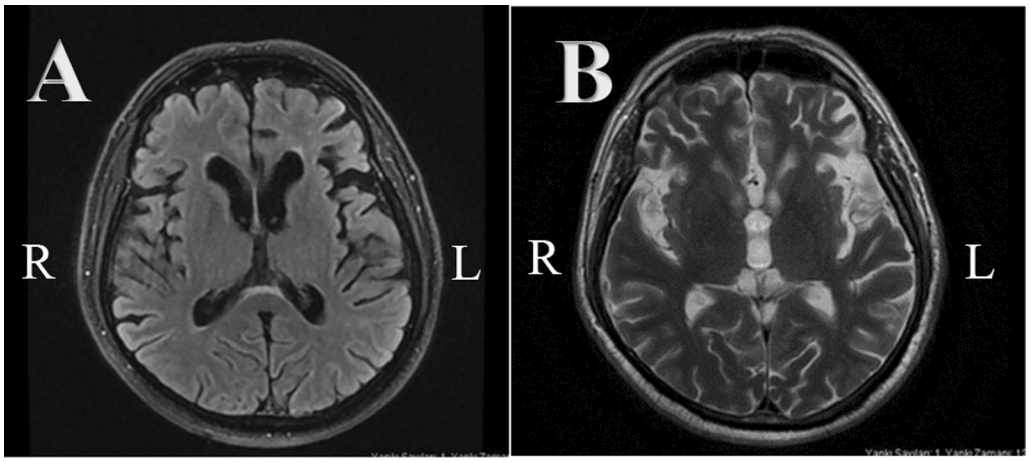

Fig. 1 T2-axial FLAIR (**A**) and T2-axial (**B**) showed cerebral sulci on the left side of the frontotemporal region and were asymmetrically deeper than those on the right

clock drawing test, the patient's planning skills were preserved.

The patient's interference time could not be evaluated because he could not complete one of the parts of the Stroop test. While the patient had eight mistakes, he had two spontaneous corrections. In line with these findings, the patient was thought to have difficulties coping with distractors.

In the verbal memory processes test, the immediate recall was three words instead of at least four words. Total learning was 63 instead of at least 107. The patient was thought to might have difficulty learning verbal material. Considering the long-term memory, the patient should have recalled 13 words. The patient might have mild-to-moderate memory impairment secondary to attention in learning the verbal material.

By evaluating visuospatial tasks, we tried to understand which parts of the brain damage caused the patient's language problems. Sublexical speech repetition is mediated by a dorsal pathway connecting the superior temporal lobe and the premotor cortices in the frontal lobe. In contrast, high language comprehension is mediated by a ventral pathway connecting the middle temporal lobe and the ventrolateral prefrontal cortex. Functions in the ventral pathway, examined with the Benton Facial Recognition Test, suggested that there were also minimum impairments in this area. The patient scoring 12 out of 30 in the Benton Judgement of Line Orientation test measuring dorsal pathway functions was observed to have mild impairments in this area.

Considering the patient's Language Assessment Test for Aphasia scores, there was a significant decrease in the spontaneous speech and language assessment. Auditory comprehension and repetition subtests were accomplished. He was found to have anomia.

The patient was started on risperidone 1 mg/day because of his psychotic symptoms. After 2 months, it was reduced to 0.5 mg due to sedation. The severity of the patient's psychotic symptoms decreased after risperidone treatment. Donepezil 10 mg/day was started again by the neurologist to whom he had previously applied for dementia symptoms. Paranoid symptoms appeared 2 months after donepezil was started.

Donepezil was discontinued, and quetiapine and risperidone were started to control behavioral and psychotic symptoms. Risperidone 0.5 mg/day treatment was terminated since it was stated that the patient's delusions had disappeared entirely in the control examination 15 days later. The quetiapine dose was gradually increased to 100 mg/day. The neurology consultation was held 3 months later, and donepezil 10 mg/day and memantine 7.5 mg/day were added to the treatment. Donepezil had discontinued again when the patient presented to the emergency department with complaints of excessive sedation and hypotension. Quetiapine was also discontinued, and aripiprazole 5 mg/day treatment was started instead. One month later, a partial increase in the patient's speech was observed at the follow-up examination. His emotional lability, senseless laughter, and perseverance were somewhat diminished. However, the clinical picture progressed within months. He received speech therapy for aphasia within one year of follow-up but did not see any significant benefit. His aphasia progressed, his apraxia developed, and his functionality gradually decreased.

Our case met the international consensus criteria for behavioral variant FTD (FTDC) published in 2011

[8] and the criteria for 'mild behavioral and/or cognitive impairment in bvFTD (MBCI-FTD) recommended in 2022 [9]. Three of the six criteria were sufficient for diagnosing possible bvFTD, while our patient met all of these criteria. In the first 3 years, he showed behavioral disinhibition, apathy and inertia, loss of empathy and sympathy, perseverative, stereotyped speech, hyperorality, sugar preferences, and deficits in executive tasks. In addition, he met the criteria for significant functional loss and frontal and anterior temporal atrophy on MRI and Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET for probable bvFTD. No genetic or histopathological evaluation was made for definite FTD. The diagnosis of bvFTD could not be made because other non-degenerative nervous systems or medical disorders better account for the exclusion criteria of a pattern of deficits. Although there was a family history of dementia and no evidence of Alzheimer's disease was found in the genetic analysis, we could not evaluate it as bvFTD because Tau specific to FTD was not determined, and the symptoms developed after a period of hypoxia in mountain climbing. We predict that this picture develops as a neurodegenerative process in the brain exposed to hypoxia.

The human organism cannot avoid a decrease in oxygen saturation in the central nervous system despite increased central blood flow associated with vasodilation, polycythemia, and hypoxia in high or extreme altitude conditions. When neurons are deprived of oxygen, they catabolize themselves. Emerging accumulation of catabolic products such as lactic acid causes irreversible damage, eventually resulting in cell death [10]. In addition to acute severe hypoxic events such as CO poisoning and asphyxia, the cumulative effect of many factors is required for milder hypoxic states to result in neurodegeneration. Neurodegenerative diseases, which start with a complex interaction of genetic predisposition, environmental factors, infections, diet, and lifestyle, follow a pathophysiological process progressing with the prodromal phase, onset, neurodegeneration, and functional loss [11]. It seems that a high risk of dementia and neurodegenerative processes can be monitored through some criteria that evaluate the loss of functional integrity of memory systems based on frontal and hippocampal regions and related cognitive disorders. Biomarkers such as kynurenic acid, EEG biomarkers, variables of neurovisceral components of fear, working memory, mitochondrial DNA, and neuroimaging are helpful indicators in evaluating risk, diagnosis, disease course, and therapeutic outcomes of neurodegenerative diseases [12]. According to Thayer's "neurovisceral integration model", heart parameters such as heart rate (HR) and heart rate variables (HRV), which reflect the suppressive function of the prefrontal cortex on the sympathetic nervous system in the central autonomic network that maintains the adaptive regulatory function of the brain, can also be used to evaluate the functions of the PFC [13].

In neuroimaging studies, the most damaged structures in hypoxic conditions were observed to be the hippocampus, cortex, and corpus striatum [14]. Bedard and colleagues suggested that the frontal lobe is also affected in people suffering from continuous hypoxia [15]. Considering McFarland's studies, while only minimal impairment is detected at low altitudes, more complex processes such as arithmetic and decision-making have been determined to be increasingly affected when climbing higher altitudes [16].

Most central nervous system symptoms of altitude diseases heal spontaneously after landing. Long-term neuropsychiatric sequelae have rarely been reported so far [5]. Whether exposure to hypoxia at high altitudes causes, irreversible brain damage is still debatable. In their MRI study with 35 mountaineers, Fayet and colleagues reported that only 10 had normal MRI findings after climbing. Twenty-five mountaineers had irreversible subcortical lesions, cortical atrophy, and enlarged Virchow–Robin spaces [1]. Two cases of high-altitude cerebral edema and subsequently developing irreversible subcortical dementia have been published in the literature [5]. Jeong and colleagues published a case mentioning personality changes after climbing 4700 m. The findings of cortical atrophy and white matter hyperintensities in mountaineers climbing to altitudes between 4810 and 8848 m were observed in MRI studies [17]. Subcortical white matter lesions have also been reported after repeated exposure to non-hypoxic hypobaria [18].

High-altitude cerebral edema and hypoxia are the causes of cognitive impairment and dementia related to white matter pathology. The literature has reported that frontal cortex dysfunction associated with white matter lesions has a probability of contributing to the clinical picture of some cases of psychosis. Specifically, frontal and temporal white matter lesions have been associated with personality changes [19]. There is also clear evidence that white matter hyperintensities bring about cognitive impairments and play a role in the etiology of dementia [20].

Frontotemporal dementia (FTD) is a clinical picture characterized by significant personality changes such as deterioration in social relations, inappropriate affect, emotional blunting, poor insight, compulsions, and hyperorality, and in which cognitive impairment mostly occurs in the form of impaired executive functions of the frontal lobe, behavioral disinhibition, loss of social awareness, apathy/aspontaneity, stereotypical behaviors, and changes in eating habits can be observed in the

behavioral variant FTD (bvFTD) [21]. Memory and visuospatial functions, primarily affected in Alzheimer's disease, are relatively preserved [22].

The symptoms of our case started within a few months after climbing to a high altitude. Difficulty in emotional expression and deterioration in social relations were the leading findings during the onset and course of the disease. From the first months of the disease, there was a decrease in the amount of speech, perseverations, anomia, and loss of insight. The absence of significant personality changes in the early years of the clinical picture and the preservation of self-care indicate that the anterior lobe is relatively protected. However, the patient has difficulty attributing meaning to words and describing objects correctly, progressive aphasia in the form of slow and interrupted speech, suggesting that the anterior regions of the temporal lobes, which are important for language, are more prominently affected.

In bvFTD, speech and language symptoms extend to multiple language domains beyond executive dysfunction [23]. Speech and language symptoms in bvFTD may appear very early in the disease and worsen as the disease progresses. In such cases, differential diagnosis from language-dominant neurodegenerative diseases such as primary progressive aphasia becomes difficult. Based on the preservation of visuospatial processes, expected to be impaired in Alzheimer's disease, the case differs from Alzheimer's disease [21].

There is relatively limited pharmacological research on possible bvFTD and no established treatment. Although it is thought that acetylcholinesterase inhibitors (AChIs), which are used in treating behavioral symptoms of Alzheimer's disease in recent years, may also improve the behavioral symptoms of FTD, negative results may be encountered in treatment applications [24]. It has been reported that cholinergic-boosting compounds may exacerbate psychiatric symptoms in patients with FTD. Donepezil can cause behavioral worsening of FTD with its mild activation and stimulant properties. There are some reports that disinhibition, agitation, restlessness, irritability, aggression, or compulsive symptoms may exacerbate after donepezil in patients with FTD. In a study conducted with 24 patients with FTD, a worsening of the FTD inventory score and an increase in disinhibition and compulsions were found in patients using donepezil at the end of 6 months [24]. Additively, cases showing persecutory delusions and aggression related to donepezil have been published [25]. Similar to these cases, in our case, after starting donepezil, persecution delusions started, and there was an increase in meaningless speech.

This negative response of the patient to donepezil suggests that the neurodegenerative process in his brain may have a pathophysiology similar to bvFTD. The clinician should remember the need to avoid donepezil in cases of FTD-like or possible bvFTD.

Conclusion

The differential diagnosis of neurodegenerative conditions permanently affecting executive and language-related brain functions is often difficult. Especially in cases where the frontal and temporal regions are secondary, the clinical picture is similar to the primary pathologies in these regions. Therefore, the clinician should pay special attention to possible differential diagnoses when encountering patients with similar clinical features, such as Alzheimer's disease or FTD, whose definitive diagnosis can be made by histopathological or genetic analysis. Considering the possible risk factors in developing neurodegenerative processes, patients should be warned about preventable situations. For example, in our case, some precautions can be taken against hypoxic damage encountered on high climbs. When planning treatment, the clinical situation should take into account the pathophysiology of symptoms and the stage of the neurodegeneration process. Especially anticholinesterase inhibitors such as donepezil should be avoided in neurodegenerative manifestations of the frontotemporal lobe.

Machines used in this study

Electroencephalograms were obtained with NicoletOne vEEG System, manufactured by Natus Medical Incorporated, Middleton, Wisconsin, US. Brain magnetic resonance imaging scans were obtained with the magnetic resonance imaging system Siemens Magnetom Essenza 1.5T, Manufactured by Siemens AG, Munich, Germany.

Abbreviations

PCo2	Partial pressure of carbon dioxide
GABA	Gamma-aminobutyric acid
EEG	Electroencephalogram
MRI	Magnetic resonance imaging
PET/CT	Positron emission tomography/computed tomography
CO	Carbon monoxide
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
VDRL/RPR	Venereal Disease Research Laboratory/rapid plasma regain
PFC	Prefrontal cortex
FTD	Frontotemporal dementia
HRV	Heart rate variables
ApoE	Apolipoprotein E
ACh-Is	Acetylcholinesterase inhibitors

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Author contributions
HT—conceptualization, data collection, writing initial draft. SÜ—writing initial draft, editing, supervision. SK—providing neurological data. All authors read and approved the final manuscript.

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Availability of data and materials
Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate
We confirm that ethical clearance was not required for publication of this case report. We confirm that the manuscript reporting adheres to CARE guidelines.

Consent for publication
Written informed consent was obtained from the participant for publication of this case and accompanying images.

Competing interests
The authors declare that they have no competing interest.

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References

1. Fayed N, Modrego PJ, Morales H. Evidence of brain damage after high-altitude climbing by means of magnetic resonance imaging. Am J Med. 2006;119(2):168.e1-6.1.
2. Hackett PH, Roach RC. High-altitude illness. N Engl J Med. 2001;345(2):107–14.
3. Zelmanovich R, Pierre K, Felisma P, Cole D, Goldman M, Lucke-Wold B. High altitude cerebral edema: improving treatment options. Biologics. 2022;2(1):81–91.
4. Garrido E, Javierre C. Extreme altitude transient aphasia. Brit J Sports Med. 1996;30:364.
5. Usui C, Inoue Y, Kimura M, Kirino E, Nagaoka S, Abe M, et al. Irreversible subcortical dementia following high altitude illness. High Alt Med Biol. 2004;5(1):77–81.
6. Beeskow AB, Oberstadt M, Saur D, Hoffmann KT, Lobsien D. Delayed post-hypoxic leukoencephalopathy (DPHL)—an uncommon variant of hypoxic brain damage in adults. Front Neurol. 2018;9:708.
7. DiSabato DJ, Quan N, Godbout JP. Neuroinflammation: the devil is in the details. J Neurochem. 2016;139(Suppl 2):136–53.
8. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134(Pt 9):2456–77.
9. Barker MS, Gottesman RT, Manoochehri M, Chapman S, Appleby BS, Brushaber D, et al. ALLFTD consortium, proposed research criteria for prodromal behavioural variant frontotemporal dementia. Brain. 2022;145(3):1079–97.
10. Virués-Ortega J, Buela-Casal G, Garrido E, Alcázar B. Neuropsychological functioning associated with high-altitude exposure. Neuropsychol Rev. 2004;14(4):197–224.
11. Tanaka M, Vécsei L. Editorial of Special Issue. Dissecting neurological and neuropsychiatric diseases: neurodegeneration and neuroprotection'. Int J Mol Sci. 2022;23(13):6991.
12. Patil V, Madgi M, Kiran A. Early prediction of Alzheimer's disease using convolutional neural network: a review. Egypt J Neurol Psychiatr Neurosurg. 2022;58(1):1–10.
13. Thayer JF, Ahs F, Fredrikson M, Sollers JJ 3rd, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci Biobehav Rev. 2012;36(2):747–56.
14. Pichiule P, Chávez JC, Boero J, Arregui A. Chronic hypoxia induces modification of the *N*-methyl-D-aspartate receptor in rat brain. Neurosci Lett. 1996;218(2):83–6.
15. Bédard MA, Montplaisir J, Richer F, Rouleau I, Malo J. Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. J Clin Exp Neuropsychol. 1991;13(6):950–64.
16. Virués-Ortega J, Garrido E, Javierre C, Kloezeman KC. Human behaviour and development under high-altitude conditions. Dev Sci. 2006;9(4):400–10.
17. Jeong JH, Kwon JC, Chin JH, Yoon SJ, Na DL. Globus pallidus lesions associated with high mountain climbing. J Korean Med Sci. 2002;17(6):861–3.
18. Kottke R, Pichler Hefti J, Rummel C, Hauf M, Hefti U, Merz TM. Morphological brain changes after climbing to extreme altitudes—a prospective cohort study. PLoS ONE. 2015;10(10): e0141097.
19. Caixeta L. What matters in white matter dementia? Dement Neuropsychologia. 2007;1:131–9.
20. Prins ND, Scheltens P. White matter hyperintensities, cognitive impairment and dementia: an update. Nat Rev Neurol. 2015;11(3):157–65.
21. Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet. 2015;386(10004):1672–82.
22. Bott NT, Radke A, Stephens ML, Kramer JH. Frontotemporal dementia: diagnosis, deficits and management. Neurodegener Dis Manag. 2014;4(6):439–54.
23. Hardy CJ, Buckley AH, Downey LE, Lehmann M, Zimmerer VC, Varley RA, et al. The language profile of behavioral variant frontotemporal dementia. J Alzheimers Dis. 2016;50(2):359–71.
24. Mendez MF, Shapira JS, McMurtray A, Licht E. Preliminary findings: behavioral worsening on donepezil in patients with frontotemporal dementia. Am J Geriatr Psychiatry. 2007;15(1):84–7.
25. Bouman WP, Pinner G. Violent behavior-associated with donepezil. Am J Psychiatry. 1998;155(11):1626–7.

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