High Incidence of Optic Disc Swelling at Very High Altitudes

Martina M. Bosch, MD; Daniel Barthelmes, MD; Tobias M. Merz, MD; Konrad E. Bloch, MD; Alexander J. Turk, MD; Urs Hefti, MD; Florian K. P. Sutter, MD; Marco Maggiorini, MD; Maria G. Wirth, MD; Otto D. Schoch, MD; Klara Landau, MD

**Objectives:** To determine the incidence of optic disc swelling as a possible indicator of cerebral edema in a large group of healthy mountaineers exposed to very high altitudes and to correlate these findings with various clinical and environmental factors and occurrence of acute mountain sickness and high-altitude cerebral edema.

**Methods:** This multidisciplinary, prospective, observational cohort study was performed in 2005 within the scope of a medical research expedition to Muztagh Ata (7546 m [24 751 ft]) in Western Xinjiang Province, China. Twenty-seven healthy mountaineers aged 26 to 62 years participated. Medical examinations were performed in Switzerland 1 month before and 4½ months after the expedition. Ophthalmologic examinations were performed at 4 high camps (maximum elevation, 6865 m [22 517 ft]). Optic disc status was documented using digital photography. Further assessments included arterial oxygen saturation and cerebral acute mountain sickness scores.

**Results:** Sixteen of 27 study subjects (59%) exhibited optic disc swelling during their stay at high altitudes, with complete regression on return to lowlands. Significant correlation was noted between optic disc swelling and lower arterial oxygen saturation (odds ratio, 0.86 per percentage of arterial oxygen saturation; 95% confidence interval, 0.81-0.92; \( P < 0.001 \)), younger age (odds ratio, 0.95 per year; 95% confidence interval, 0.90-0.99; \( P = 0.03 \)), and higher cerebral acute mountain sickness scores (odds ratio, 2.32 per 0.1 point; 95% confidence interval, 1.48-3.63; \( P < 0.001 \)).

**Conclusion:** Optic disc swelling occurs frequently in high-altitude climbers and is correlated with peripheral oxygen saturation and symptoms of acute mountain sickness. It is most likely the result of hypoxia-induced brain volume increase.

Arch Ophthalmol. 2008;126(5):644-650

**METHODS**

**DESIGN**

This prospective observational cohort study was approved by the ethical committee of the University Hospital Zurich, Zurich, Switzerland, and adheres to the tenets of the 1982 revision of the Declaration of Helsinki. Informed written consent was obtained from all subjects before initial examinations.
SETTING

The study was performed within the scope of a multidisciplinary medical research expedition performed to investigate various aspects of physiologic adaptation to hypoxia and high-altitude–related illness during ascent to Muztagh Ata (7546 m [24 751 ft]), in Western Xinjiang Province, China, from June 12, 2005, to July 18, 2005. General and ophthalmologic baseline examinations were performed at the University Hospital Zurich (490 m [1607 ft]) 1 month before the expedition and 41⁄2 months after the expedition. The mountaineers were randomly distributed to 1 of 2 groups (16 persons each) with different ascent profiles (Figure 1). Groups 1 and 2 reached the summit within 20 and 19 days, respectively, at an average ascent rate of 190 and 200 m/d (623 and 656 ft/d), respectively.

The participants started at 3750 m (12 300 ft) and ascended to the following test altitudes: base camp (4497 m [14 750 ft]), camp 1 (5533 m [18 148 ft]), camp 2 (6265 m [20 549 ft]), camp 3 (6865 m [22 517 ft]), and the summit (7546 m [24 751 ft]). Altitudes were determined according to mean daily measured barometric pressure. Ophthalmologic examinations were performed on the subsequent day on arrival at each new test altitude and on return to base camp (base camp 2) after having reached at least camp 2.

PARTICIPANTS

Thirty-four mountaineers took part in the expedition. General exclusion criteria were any type of cardiac or respiratory disease and history of high-altitude pulmonary edema, severe AMS, or HACE that occurred at altitudes below 3500 m (11 480 ft). Thirty-two subjects aged 26 to 62 years (mean age, 43 years) with a female to male ratio of 7:25 were enrolled in the ophthalmologic study. Two mountaineers were not included because of preexisting eye disease. Five of 32 participants with incomplete data sets were excluded after the expedition.

MAIN OUTCOME MEASURE

The main outcome measure of the study was optic disc status (occurrence of swelling) documented by fundus photography performed with a digital fundus camera (Zeiss FF 450 Plus; Carl Zeiss GmbH, Oberkochen, Germany) combined with fluorescein angiography in Zurich and a portable digital fundus camera (Genesis D; Kowa Inc, Tokyo, Japan) during the expedition. Pictures were taken at same times of day, with the subject at full rest for at least 1 hour and in a sitting position.

EVALUATION OF OPTIC DISCS

All optic disc photographs of each eye at every examined altitude were randomized and evaluated in masked fashion by 3 ophthalmologists (F.K.P.S., M.G.W., and K.L.). Guidelines were the criteria for papilledema as described by Walsh and Hoyt. The optic disc of each eye was judged to be either not swollen (0 points), equivocal (1 point), or swollen (2 points). For further analysis, the sum of points for both eyes at each examination was calculated for every examiner, resulting in a score ranging from 0 to 4. The final score was determined by examiner majority of two-thirds or greater. A climber was determined to have swollen optic discs at a given test altitude when a score of 3 or 4 points was achieved. Of 384 evaluated disc photographs, 379 (99%) were judged in total agreement by all 3 examiners or in accord by 2 examiners and deviating by only 1 point by 1 examiner. In 5 optic disc photographs (1.3%), difference in judgment was 2 points by the third examiner. In these cases with 2 points of disagreement, all 3 ophthalmologists reconvened to reach consensus.

Secondary outcome measures included best-corrected visual acuity, visual field, and fluorescein angiography. Best-corrected visual acuity was measured using an Early Treatment Diabetic Retinopathy Study chart. Automated static perimetry was performed at University Hospital Zurich 1 month before the expedition and 41⁄2 months after the expedition with a full-projection perimeter (Octopus 101; Haag-Streit AG, Koeniz/Bern, Switzerland) using the dynamic strategy of the built-in G2 program. Mean deviation, loss variance, and mean sensitivity were assessed.

ADDITIONAL HIGH-ALTITUDE MEASUREMENTS

Cerebral AMS (AMS-c) scores on the Environmental Symptoms Questionnaire III were assessed daily during the expedition. The AMS-c score represents symptoms that seem to reflect altered cerebral function in conjunction with the experience of being ill. For this reason, AMS-c scores were assessed rather than those on the Lake Louise Scale, which is also widely used for altitude research. A score of 0.7 or greater reliably identifies a person with AMS and pertains to items including light-headedness, headache, dizziness, dim vision, off-coordination, gastrointestinal tract upset, and weakness. The score is calculated by the sum of all item scores (range, 0-5) multiplied by their respective factorial weight and then multiplied by 0.1927. They were unavailable for group 2 at base camp 2 because of logistics. Clinical assessment of HACE included evaluation of mental status and ataxia (heel-to-toe walking test). The symptoms were scaled from 0 (no signs) to 4 (cannot stand/coma) points. High-altitude cerebral edema was diagnosed in the presence of headache and an AMS-c score of 0.7 or greater either with change in mental status or with ataxia. Pulse oximetry was performed in the evening during quiet rest with the subject in a standing position, using a finger pulse oximeter (Onyx 9500 SportStat; Nonin Medical Inc, Plymouth, Minnesota). Stable values obtained after at least 3 minutes were recorded. Brachial artery blood pressure measurements were obtained with sphygmomanometers. Mean systemic blood pressure was calculated as follows:

Diasstolic Pressure + [1⁄2 (Systolic – Diastolic Pressure)].

Drug intake was assessed daily using personal diaries. Taking of painkillers was allowed by protocol according to the personal judgment of each participant; other medication was taken only on recommendation by a physician.
STATISTICAL ANALYSIS

Repeated-measures analysis of variance was used to assess changes at different altitudes (e.g., SaO2, visual acuity, and mean systemic blood pressure) and to compare differences among the occurrences of ODS within the 2 ascent profiles. Post hoc testing (Newman-Keuls test) was performed. Differences between visual field parameters before and after the expedition were tested using a paired t test. Multiple logistic regression analysis was used to test age, blood pressure, SaO2, and AMS-c scores as potential predictors of ODS. A 2-sided α error (P value) less than .05 was considered statistically significant. Statistical analysis was performed with commercially available software (Statistica 6; StatSoft Inc, Tulsa, Oklahoma, and SPSS 13.0; SPSS Inc, Chicago, Illinois).

RESULTS

Sixteen of 27 mountaineers (59%) were observed to have had bilateral swollen optic discs (8 climbers) or a unilateral swollen optic disc and equivocal swelling of the contralateral optic disc at least once during their stay at high altitudes. Optic disc swelling was documented in 3 of 27 mountaineers at base camp 1, 8 of 27 at camp 1, 4 of 15 at camp 1 at reascent (2 climbers had persistent swelling and 2 had new swelling), 13 of 27 at camp 2, 11 of 15 at camp 3, and 2 of 27 at base camp 2 (Figure 2 and Figure 3). The 2 climbers with persistent ODS at base camp 2 had the highest AMS-c scores (2.4 and 2.9, respectively), and 1 was diagnosed as having early HACE.

Figure 2. The left optic disc of climber 9 (group 1) appears normal at baseline examination (490 m [1607 ft]) 1 month before the expedition (A) and swollen at camp 2 (6265 m [20 549 ft]) (B). Similar changes are seen in the right optic disc of climber 5 (group 2) at baseline examination 1 month before the expedition (C) and at camp 3 (6865 m [22 517 ft]) (D).
(headache, ataxia, and AMS-c score of 2.4). Of the 17 climbers who reached the summit, at least 11 had ODS at altitudes higher than 6265 m (20 549 ft). Because of logistics, it was impossible to photograph the eyes of group 1 (11 climbers) at camp 3. No statistically significant difference was noted in the incidence of ODS between the 2 groups with different ascent profiles at corresponding altitudes (P = .28). Multiple logistic regression analysis revealed high AMS-c score (odds ratio, 2.32 per 0.1 point on AMS-c score; 95% confidence interval, 1.48-3.63; P < .001), low SaO2 (odds ratio, 0.86 per percent of SaO2; 95% confidence interval, 0.81-0.92; P < .001), and lower age (odds ratio, 0.95 per year of age; 95% confidence interval, 0.81-0.92; P < .001), to show a statistically significant correlation with ODS.

The lowest mean SaO2 was 57% at camp 3, and the highest AMS-c score was 2.9 (Figure 3); both measurements showed significant changes with altitude (P < .001 and P = .006, respectively). Of 16 climbers with ODS, 9 were diagnosed as having AMS and 7 without AMS. Early HACE was diagnosed in 2 climbers, both at camp 2, with quick resolution of symptoms after return to base camp. Best-corrected visual acuity in 27 climbers did not decrease significantly during the course of the expedition, and there was no statistically significant difference in visual fields before and after the expedition. No changes at fluorescein angiography were found after the expedition compared with the initial examinations. The average mean systemic blood pressure was 92 mm Hg, ranging from 77 to 118 mm Hg with an initial dip from 93 to 89 mm Hg at base camp 1 and a statistically significant rise to 94 mm Hg at camp 1 (P = .04). Mean blood pressure did not show further significant alterations during the expedition. There was no significant correlation between blood pressure measurements and the occurrence of ODS. Climbers 26 and 28 sustained uncontrollable headaches that did not lessen after intake of ibuprofen, without any change in mental status or ataxia. They were given acetazolamide, 250 mg, dexamethasone, 8 mg, and nifedipine, 20 mg, on the second to last day and were assisted with descent to lower altitudes within a few hours. All 3 had documented ODS at the highest tested camp, before their intake of steroids, nifedipine, or acetazolamide (Table). Climbers 9 and 35 with early HACE could descend to a lower altitude (base camp) immediately on skis, where their symptoms improved significantly and additional medication with dexamethasone was not deemed necessary. Climber 9 concurrently took acetazolamide, 250 mg, on the last day of the observation period. No significant correlation was noted between ODS and drug intake.

**COMMENT**

Optic disc swelling was a surprisingly common phenomenon in our large study group of mountaineers who climbed to very high altitudes (59%). It would, no doubt, have been higher had photography measurements been possible in group 1 at the highest camp, where disc swelling was the most common. Optic disc swelling proved to be linked to age, SaO2, and AMS-c scores.

Information on ODS at high altitudes dates back to 1969 when described by Singh et al11 in Indian soldiers stationed between 3350 m (10 988 ft) and 5490 m (18 007 ft). Optic disc swelling was observed in 28 of 1925 men receiving treatment because of AMS symptoms, most of whom exhibited signs of HACE, with headache, stupor, and coma. In some of these patients, ICP measured at lumbar puncture was found to be elevated. Cerebral edema was detected at brain biopsy, necropsy, or after trephining the skull, where brain tissue was described as bulging out of the burr holes. Houston and Dickinson12 and Dickinson et al13 also reported papilledema in patients.
with HACE. Other authors\textsuperscript{14-19} have observed occasional ODS in mountaineers with high-altitude retinopathy, a clinical entity of altitude illness including engorgement and tortuosity of the retinal vessels, and optic disc hyperemia, which develops in many individuals\textsuperscript{16} who ascend to heights above 3000 m (9840 ft). Wiedman and Tabin\textsuperscript{19} showed that 3 of 21 mountaineers who had climbed to altitudes of 7600 to 8850 m (24 928-29 028 ft) sustained persistent ODS when examined within 2 days of attaining their highest altitude. These mountaineers all had AMS, and 1 had HACE, a finding consistent with those of the current study.

A widely circulated hypothesis for the development of HACE is hypoxia leading to increased cerebral vascular blood flow and disruption of the blood-brain barrier that then provokes cerebral edema and clinical signs of HACE.\textsuperscript{20} The exact pathophysiology of AMS, including the presence of brain swelling as a causative factor, is debated in the literature.\textsuperscript{2,7,21-23} Some authors consider AMS symptoms a manifestation of hypoxia-associated subclinical brain edema,\textsuperscript{24} others\textsuperscript{1,25} found brain swelling in climbers without AMS. Kallenberg et al\textsuperscript{21} and Moroczi et al\textsuperscript{25} described a significant increase in brain volume in all of their study subjects during experimentally induced normobaric hypoxia equivalent to that experienced at an altitude of 4500 m (14 760 ft). This cerebral edema detected at magnetic resonance imaging was not related to AMS and regressed to baseline values within only 6 hours of recovery outside of the decompression chamber. Detailed examinations showed signs of overall vasogenic cerebral edema and also evidence of a cytotoxic component, especially in subjects with AMS symptoms.

At sea level, bilateral ODS with normal visual function indicates elevated ICP until proved otherwise, and is then referred to as “papilledema.” Electron microscopic studies indicate that intra-axonal swelling causes most of the tissue swelling in papilledema.\textsuperscript{26} Optic disc swelling can also occur in patients without increased ICP, as a sign of various optic neuropathies resulting from causes such as ischemia, compression, inflammation, or infiltration. In these instances, it is primarily unilateral and invariably accompanied by vision loss.

An increase in the incidence of ODS was noted with decreasing SaO\textsubscript{2} during the expedition. All of our subjects had normal fundoscopic status before and after the expedition. There were no signs of inflammation, hypertensive retinopathy, or ischemic infarction of the optic discs. Visual acuity was not reduced during the expedition. No long-lasting defects were found in visual fields or angiographic findings after the expedition. Blood volume adjustments\textsuperscript{27} (for example, increased blood viscosity caused by hypobaric hypoxia) are unlikely causes of ODS during our study in the light of the timely regression of ODS on return to base camp. Thus, all evidence isolates hypoxia-induced increase in brain and optic disc

<table>
<thead>
<tr>
<th>Climber No./Sex/Age, y</th>
<th>Arrival at Summit</th>
<th>ODS Present</th>
<th>Maximum AMS-c Score</th>
<th>HACE Present</th>
<th>Minimum SaO\textsubscript{2}, Level, %</th>
<th>Drugs Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/M/56</td>
<td>Yes</td>
<td>No</td>
<td>0.35</td>
<td>No</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>2/M/48</td>
<td>Yes</td>
<td>No</td>
<td>0.64</td>
<td>No</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>4/M/46</td>
<td>Yes</td>
<td>Yes</td>
<td>1.43</td>
<td>No</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>5/M/53</td>
<td>Yes</td>
<td>Yes</td>
<td>1.85</td>
<td>No</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>7/M/26</td>
<td>Yes</td>
<td>No</td>
<td>2.20</td>
<td>Yes</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>9/M/30</td>
<td>Yes</td>
<td>Yes</td>
<td>2.91</td>
<td>Yes</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>10/M/61</td>
<td>No</td>
<td>Yes</td>
<td>0.18</td>
<td>No</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>11/M/52</td>
<td>No</td>
<td>Yes</td>
<td>1.26</td>
<td>No</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>14/M/44</td>
<td>Yes</td>
<td>No</td>
<td>0.84</td>
<td>No</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>15/M/51</td>
<td>Yes</td>
<td>Yes</td>
<td>0.57</td>
<td>No</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>17/M/44</td>
<td>No</td>
<td>Yes</td>
<td>0.47</td>
<td>No</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>18/M/35</td>
<td>No</td>
<td>No</td>
<td>0.93</td>
<td>No</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>19/M/30</td>
<td>Yes</td>
<td>Yes</td>
<td>0.30</td>
<td>No</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>20/M/55</td>
<td>Yes</td>
<td>No</td>
<td>0.35</td>
<td>No</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>21/F/28</td>
<td>No</td>
<td>Yes</td>
<td>0.73</td>
<td>No</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>23/F/46</td>
<td>Yes</td>
<td>Yes</td>
<td>0.52</td>
<td>No</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>24/F/31</td>
<td>No</td>
<td>No</td>
<td>1.43</td>
<td>No</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>25/M/40</td>
<td>Yes</td>
<td>Yes</td>
<td>1.31</td>
<td>No</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>26/F/38</td>
<td>No</td>
<td>No</td>
<td>1.91</td>
<td>No</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>27/M/36</td>
<td>Yes</td>
<td>Yes</td>
<td>0.74</td>
<td>No</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>28/M/33</td>
<td>Yes</td>
<td>Yes</td>
<td>2.38</td>
<td>No</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>29/M/52</td>
<td>No</td>
<td>No</td>
<td>0.46</td>
<td>No</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>30/M/40</td>
<td>Yes</td>
<td>Yes</td>
<td>0.91</td>
<td>No</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>33/M/37</td>
<td>No</td>
<td>Yes</td>
<td>0.27</td>
<td>No</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>35/F/48</td>
<td>No</td>
<td>No</td>
<td>1.55</td>
<td>Yes</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>36/M/53</td>
<td>No</td>
<td>No</td>
<td>1.26</td>
<td>No</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>38/F/40</td>
<td>Yes</td>
<td>Yes</td>
<td>0.27</td>
<td>No</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AMS-c, cerebral acute mountain sickness; HACE, high-altitude cerebral edema; ODS, optic disc swelling; SaO\textsubscript{2}, arterial oxygen saturation.
volume as the primary cause of ODS without necessarily evoking an increase in ICP. This mechanism explains the quick resolution of the brain swelling after descent to lower altitudes in most of the affected mountaineers. In addition, brain swelling may induce an increase in ICP\textsuperscript{5,6} and, thus, perpetuate disc swelling by causing stasis of axoplasmic flow from the optic disc to the retrolaminar myelinated optic nerve.\textsuperscript{26}

Our subjects with higher AMS-c scores had a significantly higher incidence of ODS. This may support the pathophysiologic hypothesis of malaise at high altitudes being caused by cerebral swelling. Many of our climbers with ODS were not diagnosed as having AMS. This may be because of the subjective nature of the score acquisition or because of lack of subjective impairments at high altitudes even though the climbers demonstrated cerebral changes. In the present study, only a small percentage of climbers were diagnosed as having early HACE, most probably a phenomenon related to the slow and safe\textsuperscript{1,2,3} ascent profile chosen. Furthermore, climbers older than 50 years are reported to be less prone to develop AMS than are younger climbers.\textsuperscript{29,30} This has been attributed to an age-related change in the ratio of cranial cerebrospinal fluid to brain volume, which is associated with more space for brain expansion without compression of venous outflow channels, which occurs with increasing age, and, thus, with diminished risk of increased ICP.\textsuperscript{31} Inasmuch as age was associated with lower AMS-c scores and lower incidence of ODS in our study, our results support this hypothesis. They also agree with the findings of Kallenberg et al\textsuperscript{21} and Mórocz et al\textsuperscript{25} achieved in decomposition chamber studies that brain swelling occurs in a large percentage of climbers who do not develop signs of the potentially fatal HACE. In our study, lack of rapid resolution of ODS was noted in the 2 mountaineers with the most severe AMS, 1 even diagnosed as having early HACE. Climbers who are sicker at high altitudes seem to show more persistent cerebral edema\textsuperscript{21} with probable ICP elevation and, thus, slow regression of ODS.

Comprehensive testing of neurologic factors is difficult at high altitudes for a number of reasons. Our study limitations included unavailability of ancillary testing at high altitudes including lumbar puncture or magnetic resonance imaging. Unforeseen weather changes impeded complete data collection. Because HACE occurred only in a few climbers, no statement on predictability can be made. Further research to measure ICP and evaluate its correlation to the extent of ODS is needed.

Considering the limited capacity of the craniocerebral system to compensate for an increase in brain volume and the possibly disastrous effects of elevated ICP, any indication of cerebral edema must be taken seriously. Optic disc swelling, potentially indicating brain edema, is a surprisingly common finding in high-altitude climbers even when symptoms of AMS or HACE are absent. Exposure to high altitudes seems to challenge the compensatory mechanisms for regulating ICP. Therefore, extreme caution should be the highest priority when climbing the world’s highest mountains.

Submitted for Publication: September 19, 2007; final revision received November 5, 2007; accepted November 17, 2007.

Correspondence: Martina M. Bosch, MD, Department of Ophthalmology, University Hospital Zurich, Frauenklinikstrasse 24, 8091 Zurich, Switzerland (martina.boesch@bluewin.ch).

Author Contributions: Dr Bosch had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bosch, Barthelmes, Merz, Bloch, Maggiorini, and Landau. Acquisition of data: Bosch, Barthelmes, Merz, Bloch, Turk, Hefti, Sutter, Wirth, and Schoch. Analysis and interpretation of data: Bosch, Barthelmes, Merz, Bloch, Maggiorini, Wirth, and Landau. Drafting of the manuscript: Bosch, Barthelmes, Merz, Turk, and Sutter. Critical revision of the manuscript for important intellectual content: Bosch, Barthelmes, Merz, Bloch, Hefti, Sutter, Maggiorini, Wirth, Schoch, and Landau. Statistical analysis: Bosch, Barthelmes, Merz, Bloch, and Maggiorini. Obtained funding: Bosch, Barthelmes, Merz, Bloch, Maggiorini, and Landau. Administrative, technical, and material support: Bosch, Barthelmes, Merz, Bloch, Turk, Hefti, Sutter, and Landau. Study supervision: Bosch, Barthelmes, Merz, and Landau.

Financial Disclosure: None reported.

Funding/Support: This study was supported by research grant EK 111146 from the Swiss National Research Science Foundation, by a research grant from Pfizer Inc, and a private donation to the Department of Ophthalmology, University Hospital of Zurich.

Additional Contributions: Thomas Hess, MD, Timothy A. Holmes, BS, Frederic Truffer, MS, and Gregor Schubiger, MD, provided invaluable help on Muztagh Ata.

**REFERENCES**


5. Kelle G. An account of the appearances observed in the dissection of two of three individuals presumed to have perished in the storm of the 3rd, and whose bodies were discovered in the vicinity of the Leith on the morning of the 4th of November 1821, with some reflections on the pathology of the brain. *Trans Med Chir Soc Edinb*. 1824;1:84-169.


