Optic nerve sheath diameter correlates with the presence and severity of acute mountain sickness: evidence for increased intracranial pressure

Peter J. Fagenholz, Jonathan A. Gutman, Alice F. Murray, Vicki E. Noble, Carlos A. Camargo Jr, and N. Stuart Harris

1Himalayan Rescue Association, Pheriche Clinic, Spring Season 2006, Nepal; 2Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts; 3Division of Medical Oncology, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, Washington; 4Emergency Department, New Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; and 5Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

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Fagenholz PJ, Gutman JA, Murray AF, Noble VE, Camargo CA Jr, Harris NS. Optic nerve sheath diameter correlates with the presence and severity of acute mountain sickness: evidence for increased intracranial pressure. J Appl Physiol 106: 1207–1211, 2009. First published December 31, 2008; doi:10.1152/japplphysiol.01188.2007.—Increased intracranial pressure is suspected in the pathogenesis of acute mountain sickness (AMS), but no studies have correlated it with the presence or severity of AMS. We sought to determine whether increased optic nerve sheath diameter, a surrogate measure of intracranial pressure, is associated with the presence and severity of AMS. We performed a cross-sectional study of travelers ascending through Pheriche, Nepal (4,240 m), from March 3 to May 14, 2006. AMS was assessed using the Lake Louise score. Optic nerve sheath diameter was measured by ultrasound. Ultrasound exams were performed and read by separate blinded observers. Two-hundred eighty-seven subjects were enrolled. Ten of these underwent repeat examination. Mean optic nerve sheath diameter was 5.34 mm [95% confidence interval (CI) 5.18–5.51 mm] in the 69 subjects with AMS vs. 4.46 mm (95% CI 4.39–4.54 mm) in the 218 other subjects (P < 0.0001). There was also a positive association between optic nerve sheath diameter and total Lake Louise score (P for trend < 0.0001). In a multivariate logistic regression model of factors associated with AMS, optic nerve sheath diameter was strongly associated with AMS (odds ratio 6.3; 95% CI 3.7–10.8; P < 0.0001). In 10 subjects with repeat examinations, change in Lake Louise score had a strong positive correlation with change in optic nerve sheath diameter (R² = 0.84, P < 0.001). Optic nerve sheath diameter, a proxy for intracranial pressure, is associated with the presence and severity of AMS.

Acute mountain sickness (AMS) is a syndrome occurring after ascent to high altitude, consisting of headache in conjunction with gastrointestinal symptoms (anorexia, nausea, or vomiting), sleep disturbance, dizziness, lassitude, or fatigue (12, 20). AMS was described more than 2,000 years ago and remains the most common form of altitude illness, occurring in tens of millions of people annually (11, 16, 25). AMS is initiated by exposure to hypoxia and increases with the severity of hypoxic exposure/altitude. AMS is believed by many to result from increased intracranial pressure (ICP) caused by hypoxia-induced increases in brain volume, either due to cerebral edema or dilation of cerebral blood vessels (3, 12, 25). Although this is a long-standing hypothesis, a correlation between increased ICP and the symptoms of AMS has not yet been demonstrated. Studies using both animal and human models and methods as varied as lumbar puncture, tympanic membrane displacement, computed tomography (CT), optic disc digital photography, and magnetic resonance imaging have been thwarted by small numbers or techniques poorly suited to detecting small or moderate changes in ICP (7, 8, 15, 16, 19, 21, 23, 28). Optic nerve sheath ultrasonography (ONSU) allows measurement of optic nerve sheath diameter (ONSD), which correlates with ICP, thus providing a sensitive, noninvasive surrogate measure of ICP (4, 5, 9, 10, 13, 14, 18, 22, 24, 26). The physiological basis of this technique is that increases in ICP are transmitted by the cerebrospinal fluid down the perineural subarachnoid space of the optic nerve, causing an expansion of the nerve sheath that can be measured by ultrasound. Increases in ICP cause increases in ONSD. In the largest study to date examining ICP changes in AMS, we applied this technique to a population of high-altitude travelers in Pheriche, Nepal (4,240 m), to determine if increased ICP was associated with the presence and severity of AMS.

Materials and Methods

Participants. Travelers ascending through Pheriche, Nepal (4,240 m), from March 3 to May 14, 2006, were recruited by local advertisement and direct daily solicitation by investigators. All adults who had not slept higher than Pheriche for 2 wk preceding participation and had no history of intracranial tumor or surgery, recent ocular trauma, or evidence of high-altitude cerebral or pulmonary edema were eligible. Repeat examination was performed on 10 participants when they returned to the clinic as visitors (n = 6) or patients (n = 4) and agreed to participate again. Planned repeat examination was not required for initial enrollment. Because many subjects undergoing repeat examination slept higher than Pheriche between their initial and repeat exams and thus would not have been eligible for initial enrollment, repeat examinations were not included in the aggregate analysis of initial exams but were only considered relative to each subject’s initial examination. Written informed consent was obtained from all subjects; translators were employed when necessary. The study was approved by the Massachusetts General Hospital’s institutional review board and the Nepal Health Research Council.

Procedures. After enrollment, one investigator performed an examination, obtaining information on demographics, ascent history, and vital signs, and assigning a Lake Louise score (LLS), a standard
scoring system for AMS research, based on a review of all component signs and symptoms (20). Lake Louise points were assigned on a 0 to 3 scale for headache, gastrointestinal symptoms, fatigue, dizziness, difficulty sleeping, and mental status; and 0 to 2 for peripheral edema and ataxia (20).

Subjects then underwent ONSU by a second investigator masked to the results of the initial exam, including LLS. All ONSU exams were performed by the same investigator using the standard technique described in the literature (4, 5, 18, 24, 26). In brief, subjects were positioned supine with eyes closed. An adhesive plastic dressing was applied over the closed eyelid. Conductive ultrasound gel was applied to the dressing, and a portable ultrasound machine (Sonosite 180 plus, Sonosite, Seattle, WA) with a 7- to 10-MHz transducer was used to acquire a longitudinal, cross-sectional image of the optic nerve posterior to the orbit (Fig. 1). Three images were obtained from each eye of each subject to minimize intraobserver variability (1).

Images were saved and transferred to a personal computer where a third investigator, blinded to the subject and LLS, measured the diameter of the optic nerve 3 mm posterior to the globe. Measurements were made using IrfanView 3.31 (Irfan, Skiljan, Austria) by identifying the coordinates (x,y) of the optic nerve sheath borders and using these coordinates to calculate ONSD. Performing post hoc measurements by this method allowed multiple readers to review each image in blinded fashion and allowed greater precision than is possible using the on-screen calipers to make measurements at the time of ultrasonography. The arithmetic mean of the ONSD measured in all six images was calculated to yield a mean ONSD for each subject. To address potential interobserver differences in ONSD readings, a second blinded investigator measured the ONSD of 40 randomly selected subjects.

Statistical analysis. The main outcome measures were the difference in mean ONSD between subjects with and without AMS; the association between ONSD and AMS status in multivariate analysis (with age, sex, ascent rate, oxygen saturation, and heart rate as prespecified covariates); the association between ONSD and each individual Lake Louise score component; and the change in ONSD with change in LLS. All outcomes were prospectively planned.

All subjects with a headache and LLS ≥3 were considered to have AMS (20, 27). Average ascent rate after arrival at high altitude was calculated by dividing the total altitude gained between the start of ascent and arrival in Pheriche by the number of days required to make the ascent. Comparisons were made using paired Student’s t-test or Wilcoxon signed-rank test, as appropriate. Chi-square for trend was used to assess trends within given variables. Correlation was assessed using Spearman’s correlation coefficient. Multivariate logistic regression was used to evaluate factors associated with AMS status (yes/no), while multivariate linear regression was used to examine ONSD. The covariates in each model were prespecified. All data were analyzed using STATA 9.0 (Stata Corp, College Station, TX).

Analysis of the interobserver agreement data showed that the values from each observer were correlated (Spearman’s r = 0.74, P < 0.001). A Bland-Altman plot showed a mean difference between observers of 0.33 ± 0.53 mm (6).

RESULTS

We enrolled 287 subjects in our study, 69 (24%) with AMS and 218 (76%) without AMS. Demographic and clinical characteristics of these groups are presented in Table 1. Fourteen subjects began their ascent in Jiri (1,935 m), 267 in Lukla (2,850 m), and 6 in Namche (3,450 m). Fifty-one subjects were taking acetazolamide at the time of participation, 12 were taking acetaminophen, 12 ibuprofen, 3 aspirin, 2 ginkgo, and 1 dexamethasone. The mean ONSD in subjects with AMS was 5.34 mm [95% confidence interval (CI) 5.18–5.51 mm] vs. 4.46 mm (95% CI 4.39–4.54 mm) in subjects without AMS (Student’s t-test P < 0.001). Figure 2 shows the positive trend in ONSD starts at a Lake Louise score of 3, the threshold for acute mountain sickness (AMS). Whiskers denote the SD. For all data, P for trend < 0.001.

Table 1. Demographic and clinical characteristics of subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AMS (n = 69)</th>
<th>No AMS (n = 218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*, yr</td>
<td>36.6 (12.4)</td>
<td>36.4 (11.5)</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>51 (74%)</td>
<td>146 (67%)</td>
</tr>
<tr>
<td>Oxygen saturation*, %</td>
<td>84.0 (4.4)</td>
<td>87.6 (4.5)</td>
</tr>
<tr>
<td>Heart rate*, beats/min</td>
<td>89.4 (14.2)</td>
<td>83.0 (15.2)</td>
</tr>
<tr>
<td>Average ascent rate after arrival at high altitude*, m/day</td>
<td>272 (120)</td>
<td>237 (55)</td>
</tr>
<tr>
<td>Nationality of nations with &gt;20 participants†, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>20 (29%)</td>
<td>49 (22%)</td>
</tr>
<tr>
<td>USA</td>
<td>8 (12%)</td>
<td>40 (18%)</td>
</tr>
<tr>
<td>Australia</td>
<td>4 (6%)</td>
<td>22 (10%)</td>
</tr>
<tr>
<td>Nepal</td>
<td>13 (19%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Ireland</td>
<td>6 (9%)</td>
<td>14 (6%)</td>
</tr>
</tbody>
</table>

*Values are means (SD). †Nations with 20 or more participants are listed in table in order of total participants. Nations with <20 participants are Austria, Belgium, Canada, Chile, the Czech Republic, Denmark, Finland, Germany, France, Greece, Holland, Israel, Italy, Malaysia, New Zealand, Poland, Russia, Singapore, South Africa, Spain, Sweden, and Switzerland. AMS, acute mountain sickness.

Fig. 1. Sample optic nerve sheath ultrasonography image.

Fig. 2. Relationship between Lake Louise score and optic nerve sheath diameter (ONSD). Data from 287 subjects in Pheriche, Nepal. The upward trend in ONSD starts at a Lake Louise score of 3, the threshold for acute mountain sickness (AMS). Whiskers denote the SD. For all data, P for trend < 0.001.
association between ONSD and total LLS \[P \text{ (chi-square)} \text{ for trend} < 0.001\]. Figure 3 shows the positive association between ONSD and most of the individual LLS components: headache, gastrointestinal symptoms, fatigue, dizziness, difficulty sleeping, and ataxia. ONSD had a borderline significant association with mental status \((P = 0.06)\), and no association with peripheral edema \((P = 0.21)\). Peripheral edema is the only component of the Lake Louise score not considered a clinical symptom of AMS. No subject had more than 2 Lake Louise points for any symptom.

Ten patients underwent repeat examination; one of these patients developed AMS between exams, two had AMS resolve, two had persistent AMS at both exams (although 1 of these had an 11-point increase in LLS), and five had no AMS at the time of either exam. The relationship between the change in LLS and change in ONSD between exams is depicted in Fig. 4. There was a strong positive correlation between change in LLS and change in ONSD \(\left(R^2 = 0.84, P < 0.001\right)\).

In subjects taking acetazolamide, 17 suffered from AMS at the time of evaluation and 34 did not. The mean ONSD in those with AMS was 5.35 mm \(95\% \text{ CI} 5.04–5.66\) mm vs. 4.61 mm \(95\% \text{ CI} 4.42–4.81\) mm in those without AMS \(\text{Student’s} t\)-test \(P < 0.001\).

**DISCUSSION**

Our results demonstrate a positive association between ONSD and the presence and severity of AMS in a large, heterogeneous population of travelers to high altitude. This association was significant in both a large cross-sectional...
study and in a smaller sample of subjects undergoing repeat examination. Given the recently established correlation between ONSD and ICP (4, 5, 9, 10, 13, 14, 18, 22, 24, 26), the large sample size, and the statistical significance of our results, we believe these data provide compelling evidence supporting a role for increased ICP in the pathogenesis of AMS.

Increased ICP in AMS likely occurs due to increases in brain volume. Although brain volume changes have been noted on ascent to high altitude, these have never been definitively linked with the presence of AMS (2, 8, 17, 23). The cause of these increases, whether from cerebral edema or increases in the volume of cerebral blood flow due to hypoxia-induced vasodilation, is not clear. Evidence exists to support both hypotheses (2, 17, 25). Our study was not designed to differentiate between these or other possible mechanisms or to establish a causal relationship between increased ICP and AMS. Nevertheless, the strong association between ONSD and AMS symptoms presented here, in the cohort as a whole and in the subgroup taking acetazolamide, provides compelling evidence that increased ICP is involved in the dominant pathophysiological pathway in AMS.

The primary limitation of this study is that we did not obtain baseline low-altitude measurements or repeat measurements on most of our subjects. A study involving repeated ONSD measure before, during, and after a controlled hypoxic exposure, and providing correlation with AMS symptoms could help further define the importance of ONSD and ICP changes in the pathophysiology of AMS. Nonetheless, the results from repeat measurements we did obtain, although they rely heavily on three subjects with large changes in LLS and ONSD, are compelling and support our inferences from the large cross-sectional study. The large size of our cohort and the statistical significance of our results imply that the ONSD differences we describe between subjects with and without AMS are importantly linked to AMS status. Another limitation of our data relates to the technique of ONSU. While evidence continues to accrue that ONSD correlates with ICP (4, 5, 9, 10, 13, 14, 18, 22, 24, 26), it is possible that other factors, such as cerebral edema, may independently affect ultrasonographically measured ONSD. In this case, the relationship we describe between ONSD and AMS may be dependent on more than just ICP changes. Also, it is difficult at this point to correlate specific ONSDs as measured by ONSU with exact ICP. Different investigators have advanced different ONSDs, usually in the 5- to 6-mm range, as likely to represent increased ICP (1, 18). The degree of ICP increase our ONSD data may represent cannot be precisely defined. It is possible refinements in the technique will help to overcome this limitation in future studies.

In summary, the noninvasive technique of ONSU is feasible in remote, high-altitude locations and could provide an important new technique for research, diagnosis, and monitoring of AMS. Measurement of ONSD has a stronger association with the presence and severity of AMS than any prior assessment tool. Our findings provide compelling evidence for the long-suspected but never demonstrated association between increased ICP and the symptoms and severity of AMS. This correlation may provide fundamental pathophysiological insights and help guide future research into the etiology, prevention, and treatment of this common disorder.

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20. Lake Louise Consensus Committee. The Lake Louise consensus on the definition and quantification of altitude illness. In: Hypoxia and Molecular


