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CLINICAL RESEARCH STUDY

# Hyponatremia in Marathon Runners due to Inappropriate Arginine Vasopressin Secretion

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## ABSTRACT

**PURPOSE:** Exercise-associated hyponatremia (EAH), as defined by a blood sodium concentration [ $\text{Na}^+$ ] less than 135 mmol/L, may lead to hypotonic encephalopathy with fatal cerebral edema. Understanding the pathogenic role of antidiuresis may lead to improved strategies for prevention and treatment.

**METHODS:** Normonatremic marathon runners were tested pre- and post-race for creatine kinase, interleukin-6, cortisol, prolactin, and arginine vasopressin. Similar testing also was carried out in runners with encephalopathy caused by EAH, including 2 cases with fatal cerebral edema.

**RESULTS:** Normonatremic runners ( $n = 33$ ; 2001) with a mean 3% decrease in body weight showed a 40-fold increase in interleukin-6 ( $66.6 \pm 11.9$  pg/mL from  $1.6 \pm 0.5$  pg/mL,  $P = .001$ ), which was significantly correlated with increases in creatine kinase ( $r = 0.88$ ,  $P < .0001$ ), cortisol ( $r = 0.70$ ,  $P = .0003$ ), and prolactin ( $r = 0.67$ ,  $P < .007$ ), but not arginine vasopressin ( $r = 0.44$ ,  $P = .07$ ). Collapsed runners with EAH ( $n = 22$ ; 2004) showed a mean blood urea nitrogen less than 15 mg/dL with measurable plasma levels of arginine vasopressin ( $>0.5$  pg/mL) in 43% of cases. Two marathon runners with fatal cerebral edema additionally showed less than maximally dilute urines ( $>100$  mmol/kg/ $\text{H}_2\text{O}$ ) and urine [ $\text{Na}^+$ ] greater than 25 mEq/L.

**CONCLUSIONS:** Cases of EAH fulfill the essential diagnostic criteria for the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Runners with hypotonic encephalopathy at subsequent races were treated with intravenous hypertonic (3%) saline on the basis of this paradigm, which resulted in rapid clinical improvement without adverse effects. Release of muscle-derived interleukin-6 may play a role in the nonosmotic secretion of arginine vasopressin, thereby linking rhabdomyolysis to the pathogenesis of EAH. © 2007 Elsevier Inc. All rights reserved.

**KEYWORDS:** Arginine vasopressin; Exercise-associated hyponatremia; Hypertonic (3%) saline; Interleukin-6; Rhabdomyolysis; Syndrome of inappropriate antidiuretic hormone secretion

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Exercise-associated hyponatremia (EAH) is defined by a blood sodium concentration [ $\text{Na}^+$ ] less than 135 mmol/L during or after prolonged physical exertion. This condition, which has been shown to occur in 13% of recent Boston marathon runners, has resulted in life-threatening hypotonic encephalopathy and fatal cerebral edema at multiple races.<sup>1-6</sup> A recent Consensus Statement determined EAH to be dilutional in nature, although the relative contributions of excess fluid intake and antidiuresis could not be differentiated by the evidence available at

that time.<sup>7</sup> Extending prior studies on inflammation related to rhabdomyolysis,<sup>8-10</sup> we analyzed the potential association between muscle-derived interleukin-6 and neuroendocrine mediators related to body fluid homeostasis.<sup>11-13</sup> Findings in runners with EAH, including 2 cases with fatal cerebral edema, satisfied the essential criteria for the syndrome of inappropriate antidiuretic hormone secretion (SIADH) as established in 1967.<sup>14</sup> On the basis of this paradigm, intravenous hypertonic (3%) saline was used as a well-validated treatment in cases of life-threatening hypotonic encephalopathy.

## SUBJECTS AND METHODS

Thirty-three runners with a mean age of  $49 \pm 10$  years (standard error) participated in studies at the 2001 Boston marathon that were approved by the institutional review board of McLean Hospital, Belmont, Massachusetts. Blood samples were tested for creatine kinase, interleukin-6, arginine vasopressin, cortisol, prolactin, and C-reactive protein on the day before and within 2 hours post-race with 11 subjects providing a next-day sample. Whole-blood samples were analyzed on the Roche/Hitachi 917 system (Roche Diagnostics, Indianapolis, Ind), frozen at  $-70^{\circ}\text{C}$ , and subsequently tested by radioimmunoassay for interleukin-6 by Quantikine High Sensitivity/HS (R & D Systems, Inc, Minneapolis, Minn); C-reactive protein by IMMULITE High-Sensitivity CRP (Diagnostics Products Corporation, Los Angeles, Calif); arginine vasopressin by GammaCoat <sup>125</sup>I RIA Kits (DiaSorin Corporation Stillwater, Minn); and cortisol and prolactin by ImmChem <sup>125</sup>I RIA Kits, ICN Biomedicals, Inc (Costa Mesa, Calif). All results are reported as means  $\pm$  standard error of the mean. Two-tailed Student *t* tests were used to compare pre- and post-race changes.

Blood samples obtained from collapsed runners in the medical tent at the 2004 Boston marathon ( $n = 308$ ) in lithium heparin tubes were immediately analyzed on Stat Profile M7 using reagents and trained personnel provided by the manufacturer (Nova Biomedical, Waltham, Mass). Samples were frozen at  $-70^{\circ}\text{C}$  and subsequently analyzed for interleukin-6 by IMMULITE and arginine vasopressin by a radioimmunoassay using previously published methods.<sup>15,16</sup> A subset of these tests also was performed on stored blood samples in 2 marathon runners with fatal cerebral edema after obtaining consent from the next of kin.

Results are reported as means  $\pm$  standard error of the mean. Pearson and Spearman correlation coefficients were calculated using standard methods with significance set at a *P* value less than .05.

## CLINICAL SIGNIFICANCE

- Inappropriate antidiuretic hormone secretion exists in patients with exercise-associated hyponatremia.
- Although guidelines for marathon runners advise fluid intake be guided by thirst, this may not be a reliable measure. Monitoring weight changes during races is one way to detect fluid retention, which is characteristic of exercise-associated hyponatremia.
- Headache, nausea, and vomiting—especially when accompanied by changes in mental status—are warning signs of exercise-associated hyponatremia. Mild cases can be managed by restricting fluids until the onset of urination. Manifestations of hypotonic encephalopathy indicate the need for emergent treatment with hypertonic solutions such as 3% saline or mannitol.

## RESULTS

Normonatremic runners at the 2001 Boston marathon ( $n = 33$ ) showed post-race increases in blood urea nitrogen ( $19.5 \pm 4.4$  mg/dL from  $16.0 \pm 5.5$  mg/dL,  $P < .001$ ) and serum creatinine ( $1.3 \pm 0.3$  mg/dL from  $1.0 \pm 0.2$  mg/dL,  $P = .001$ ) with a  $3.0\% \pm 0.6\%$  decrease in body weight. A 15-fold post-race increase in creatine kinase ( $2323 \pm 639$  U/L from  $150 \pm 19$  U/L,  $P < .001$ ) was correlated with a 40-fold increase in interleukin-6 ( $66.64 \pm 11.92$  pg/mL from  $1.55 \pm 0.45$  pg/mL,  $P < .0001$ ;  $r = 0.88$ ) (Tables 1 and 2). Changes in interleukin-6 also were correlated with 2-fold increases in cortisol ( $801 \pm 81$  mmol/L from  $342 \pm 28$  mmol/L,  $P = .0001$ ;  $r = 0.70$ ,  $P = .0003$ ) and prolactin ( $26.6 \pm 2.6$  ng/mL from  $11.7 \pm 1.0$  ng/mL,  $P = 0.0001$ ;  $r = .67$ ,  $P = .0005$ ), but not with arginine vasopressin ( $4.33 \pm 0.71$  pg/mL from  $2.86 \pm 0.32$  pg/mL,  $P = .03$ ;  $r = 0.44$ ,  $P = .07$ ). Interleukin-6, cortisol,

prolactin, and arginine vasopressin returned to pre-race levels the morning after the race, at which time there was a 20-fold increase in C-reactive protein ( $2.30 \pm 0.53$  mg/dL from  $0.10 \pm 0.02$  mg/dL,  $P = .01$ ).

Collapsed runners in the finish line medical tent at the 2004 Boston marathon showed a mean blood  $[\text{Na}^+]$  of  $143.0 \pm 5.5$  mmol/L ( $n = 308$ , range = 122-158 mmol/L) and mean blood urea nitrogen of  $19 \pm 4.1$  mg/dL ( $n = 66$ , range 11-29 mg/dL). Arginine vasopressin levels were  $9.47 \pm 8.57$  pg/mL in 34 collapsed runners with blood  $[\text{Na}^+]$  greater than 145 mmol/L, which is consistent with osmotic regulation of vasopressin secretion. In contrast, arginine vasopressin was measurable ( $>0.5$  pg/mL) in 7 of 16 runners (43%) with EAH (Figure 1) who had a mean blood urea nitrogen of  $14.2 \pm 2.1$  mg/dL ( $n = 5$ ). Lack of urination during treatment was observed in all runners with EAH with and without detectable arginine vasopressin levels, suggesting that a decrease in urine production rather than fluid loading was the predominant cause of the dilutional effect. Collapsed runners with EAH in whom blood urea nitrogen was measured at the 2002-2005 Boston Marathons showed a mean value of  $13.2 \pm 2.5$  mg/dL ( $n = 10$ ),

**Table 1** Results of Creatine Kinase, Interleukin, C-Reactive Protein, Cortisol, Prolactin, and Arginine Vasopressin Levels in Asymptomatic Boston Marathon Runners in 2001 (Means ± Standard Error of the Mean)

	Pre-race (n = 33)	<2 h Post-race (n = 33)	<24 h Post-race (n = 11)
Creatine kinase (U/L)	150 ± 19	745 ± 97*	2323 ± 639*
NL = 27-218 U/L			
Interleukin-6 (pg/mL)	1.6 ± 0.45	66.6 ± 11.9*	4.3 ± 0.6
NL = 0-5.0 pg/mL			
C-reactive protein (ng/dL)	0.10 ± 0.02	0.10 ± 0.03	2.30 ± 0.53*
NL = 0.0-0.5 ng/dL			
Cortisol (nmol/L)	342 ± 28	801 ± 81*	369 ± 25
NL = 70-250 nmol/L			
Prolactin (ng/mL)	11.7 ± 1.0	26.6 ± 2.6*	14.5 ± 1.4
NL = 7-18 ng/mL			
Arginine vasopressin (pg/mL)	2.86 ± 0.32	4.33 ± 0.71*	3.19 ± 0.83
NL = 1.0-13.3 pg/mL			

NL = Normal.

\*P <.05.

in contrast with a mean of 23.2 ± 5.1 mg/dL in runners with a blood [Na<sup>+</sup>] greater than 145 mmol/L (n = 20) (Table 3). Blood urea nitrogen values significantly predicted both hyponatremia and hypernatremia as a surrogate marker for extracellular fluid volume (Table 4).

Two previously healthy women aged 24 and 32 years collapsed and were unresponsive with stable vital signs after more than 4½ hours while participating as charity fundraisers in the 2002 Boston and Marine Corps marathons. Both runners were taking nonsteroidal anti-inflammatory drugs and consumed fluids at water stations at every mile with exclusive intake of Gatorade in 1 case as related by her coach and teammates. After endotracheal intubation for coma on arrival at emergency services, isotonic (0.9%) saline was initially infused at 150 mL/before serum [Na<sup>+</sup>] values of 113 and 123 mmol/L were reported. Blood urea nitrogen levels were less than 10 mg/dL, urine osmolalities were 329 and 121 mOsm/kg H<sub>2</sub>O, and urine [Na<sup>+</sup>] was 81 and 25 mEq/L, respectively. Arginine vasopressin and cortisol levels were elevated and thyroid profiles were normal in both cases. Computed tomography of the brain and chest radiography showed diffuse cerebral and pulmonary edema. Coma persisted with the onset of central diabetes insipidus as a sign of clinical brain death, which required use of

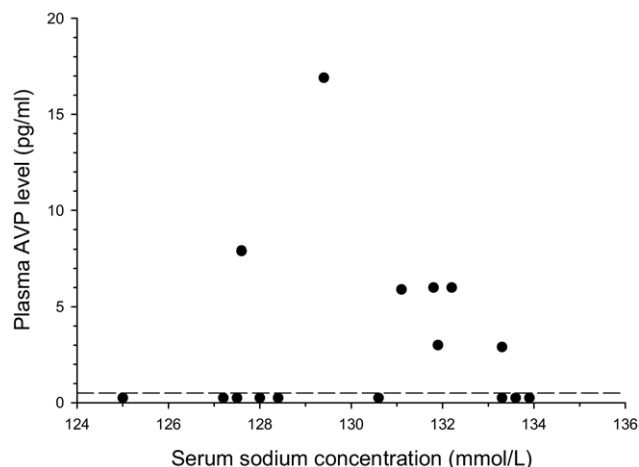
desmopressin to maintain normal serum osmolality. Diffuse cerebral edema was found at postmortem examinations without pontine or extrapontine myelinolysis. Cases of hypotonic encephalopathy were treated with intravenous hypertonic (3%) saline at the 2004-2005 Marine Corps and Boston marathons, which resulted in rapid neurologic improvement without adverse effects (Figure 2).

**DISCUSSION**

EAH has been variously attributed to sodium depletion and fluid retention, which represent opposite disturbances of body fluid homeostasis that can result in hyponatremia.<sup>17-19</sup> The finding herein that mean blood urea nitrogen was less

**Table 2** Correlations Between Interleukin-6 and Creatine Kinase, Cortisol, Prolactin, and Arginine Vasopressin in 2001 Boston Marathon Runners (Pre-marathon and Within 2 Hours Post-race (n = 33), Pre- and Within 18 Hours Post-race (n = 11))

	<2 h Post-race (n = 33)	<18 h Post-race (n = 11)
Creatine kinase	r = 0.88, P <.0001	r = 0.69, P = .002
Cortisol	r = 0.70, P = .0003	Not correlated
Prolactin	r = 0.67, P = .0007	r = 0.41, P = .06
Arginine vasopressin	r = 0.44, P = .07	Not correlated



**Figure 1** Plasma arginine vasopressin (AVP) levels measured at the end of the 2004 Boston marathon in collapsed runners with EAH ([Na<sup>+</sup>] < 135 mmol/L). \* The detection limits (dashed line) for the AVP radioimmunoassay (0.5 pg/mL). Seven of 16 runners (43%) with EAH had hypo-osmolality with measurable levels of AVP (\*22 of 308 collapsed runners were found to have EAH, but sufficient plasma samples were only available for 16 of these to allow measurement of AVP by radioimmunoassay). MCM = Marine Corps Marathon; CNS = central nervous system.

**Table 3** Blood Urea Nitrogen as a Function of Low and High [Na<sup>+</sup>] Concentrations in Collapsed Runners in the 2000-2005 Boston Marathons

	[Na <sup>+</sup> ] < 135 mmol/L	[Na <sup>+</sup> ] > 145 mmol/L
n	10	20
mean BUN, mg/dL	13.2*	23.2
SD	2.53	5.08

BUN = blood urea nitrogen; SD = standard deviation.  
\*P < .05.

than 15 mg/dL in runners with EAH is consistent with the previously reported inverse correlation of serum [Na<sup>+</sup>] and changes in body weight on which the Consensus Statement concluded that EAH is predominantly dilutional in nature.<sup>7,20</sup> Because the relative contributions from avid fluid intake and antidiuresis were not ascertainable from studies then available, we measured neuroendocrine responses related to body fluid homeostasis in relation to muscle-derived interleukin-6 released during rhabdomyolysis.<sup>8-13</sup> A 40-fold increase in interleukin-6 was significantly correlated with a 20-fold elevation in creatine kinase and 2-fold increases in cortisol and prolactin. These findings are consistent with neurohumoral stimulation by interleukin-6 accompanied by an inflammatory response to rhabdomyolysis with the next-day elevation in C-reactive protein. In contrast, arginine vasopressin stimulation was likely the result of volume depletion in runners with weight loss, which normalized serum [Na<sup>+</sup>] despite post-race increases in blood urea nitrogen and serum creatinine.<sup>5,9</sup>

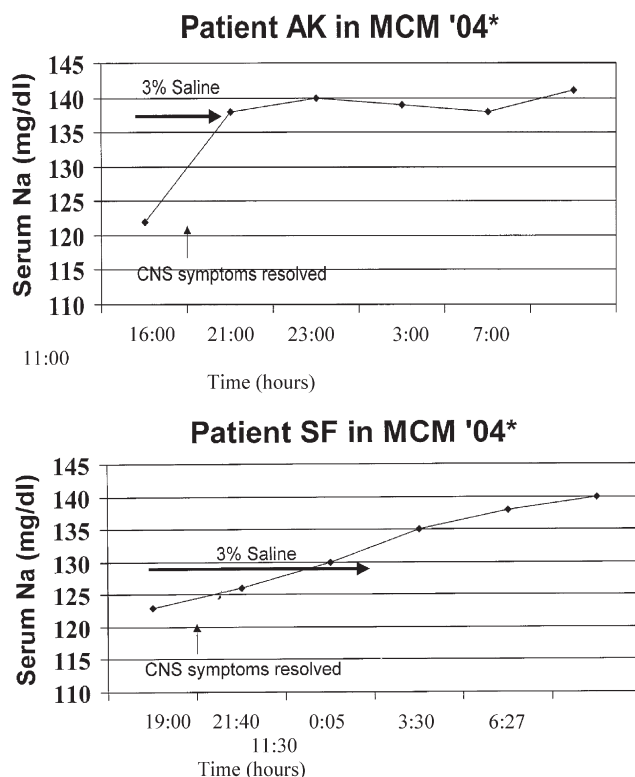
In contrast, runners with EAH were normovolemic, as indicated by blood urea nitrogen values less than 15 mg/dL. Detectable levels of arginine vasopressin (>0.5 pg/mL) in 43% of these cases are physiologically inappropriate in the presence of hypo-osmolality and are consistent with the diagnostic criteria for the syndrome of inappropriate secretion of antidiuretic hormone.<sup>21</sup> The absence of urination in cases of EAH during treatment in the medical tent indicates that vasopressin levels were sufficient to impair maximal urine free-water excretion. This clinical feature also was present in cases of EAH without measurable hormone, suggesting ex vivo proteolysis as the likely explanation for the negative findings in some specimens.

The 2 cases of fatal cerebral edema additionally showed less than maximally dilute urine (>100 mOsm/kg H<sub>2</sub>O) and

**Table 4** Probability that Blood Urea Nitrogen Predicts [Na<sup>+</sup>] Concentration (Assumes the Data Is Normally Distributed for [n<sub>A</sub> + n<sub>B</sub>]-2 Degrees of Freedom)

[Na <sup>+</sup> ] < 135 versus [Na <sup>+</sup> ] > 145 mmol/L	
BUN	Pr (x <sub>d</sub> = 10.0) < 0.0001

BUN = blood urea nitrogen.



**Figure 2** Time course of correction of hyponatremia in 2 runners with hypotonic encephalopathy during the 2004 Marine Corps marathon. Both cases presented with delirium and a serum [Na<sup>+</sup>] of 123 mmol/L. Intravenous 3% saline was administered at the rates shown, which resulted in clearing of mental status (arrows). There were no adverse effects in either patient. MCM = Marine Corps Marathon; CNS = central nervous system.

elevated urine [Na<sup>+</sup>] (>25 mEq/L) with measurable arginine vasopressin levels (>0.5 pg/mL). In combination with elevated cortisol values and normal thyroid function, these cases unequivocally fulfill all of the diagnostic criteria for SIADH, as originally described in 1967.<sup>14,21</sup> Measurable levels of arginine vasopressin clearly establish EAH as a true variant of SIADH, in contrast with the physiologic suppression of arginine vasopressin secretion generally associated with primary polydipsia and the newly described nephrogenic syndrome of inappropriate antidiuresis.<sup>22,23</sup>

The SIADH paradigm should be taken into account in designing strategies for the prevention and treatment of EAH. Although avid fluid consumption is clearly a risk factor for EAH, in most cases this behavior alone would not result in fluid retention sufficient to induce dilutional hyponatremia without a concomitant decrease in urine production. Antidiuresis might therefore be viewed as the proximate cause of EAH, whereas avid fluid consumption, or dipsomania, might be seen as a precondition.<sup>24,25</sup> The elevated urine sodium excretion in SIADH is well known to be associated with the expansion of the plasma and extracellular fluid volume before the onset of escape from antidiuresis, rather than representing true renal salt-wasting.<sup>26,27</sup> This effect may be additionally enhanced in EAH by secre-

tion of atrial natriuretic peptides, which decrease proximal sodium reabsorption because of an expanded intravascular volume.<sup>28</sup>

The presence of natriuresis in SIADH distinguishes this condition from dehydration as the primary mechanism for EAH. Salt depletion as a putative cause of EAH would result in a low urine  $[Na^+]$  from increased renal sodium reabsorption, both proximally due to decreased renal perfusion and glomerular filtration, and distally due to activation of the renin-angiotensin-aldosterone system. The view in some lay sports medicine circles that salt depletion during sweating contributes to hyponatremia suggests that sodium supplements, including electrolyte-enhanced sports drinks, may prevent and treat EAH as well as dehydration.<sup>29,30</sup> Insofar as the mechanism for water intoxication depends on a hormonally induced antidiuresis, the development of EAH would be expected to be relatively independent of changes in sodium balance.<sup>27,31</sup> In contrast to the value of salt supplements for preventing exertional dehydration,<sup>32</sup> this approach would not be expected to prevent dilutional hyponatremia resulting from avid consumption of hypotonic fluids under conditions of SIADH. Gatorade, for example, was found not to prevent or correct hyponatremia in polydipsic patients with schizophrenia, a condition mediated in part by inappropriate secretion of arginine vasopressin.<sup>33</sup> Although electrolyte-containing hypotonic beverages have been shown to decrease the rate of reduction in serum  $[Na^+]$  relative to water,<sup>34</sup> intake of such fluids even at moderate levels may not preclude the development of EAH or prevent its progression to fatal cerebral edema, as occurred in the Boston runner.<sup>35,36</sup> The pathophysiology of SIADH therefore accounts for the limitations of sodium supplements and electrolyte-enhanced sports beverages regarding the prevention and treatment of EAH.

Recently updated guidelines on fluid consumption for marathon runners advise intake guided by thirst.<sup>37</sup> Given an average finishing time approaching 5 hours among current US marathon participants,<sup>38</sup> monitoring weight changes during races, especially for slower runners, may provide an objective measure for early detection of the fluid retention characteristic of symptomatic EAH, rather than relying solely on the subjective perception of thirst. This strategy may facilitate the earlier diagnosis of EAH before progression to a 3% weight gain associated with a decrease in serum  $[Na^+]$  to less than 130 mmol/L in a recent mathematical analysis.<sup>39</sup>

The SIADH paradigm accounts for the delayed onset of EAH in runners after races who may continue avid fluid consumption under a mistaken impression that delayed urination represents persistent dehydration. This paradigm also explains an apparent increase in severity of EAH with use of nonsteroidal anti-inflammatory drugs, as has been observed in other clinical settings.<sup>40</sup> Although not shown to be an independent risk factor for EAH, these prostaglandin cyclooxygenase inhibitors are known to enhance the renal activity of

arginine vasopressin and should be avoided within 24 hours before a race.

When prevention fails, definitive diagnosis of EAH by point-of-care testing facilitates triage of symptomatic runners to appropriate treatment protocols.<sup>5</sup> Headache, nausea, and vomiting should raise the index of suspicion for EAH, especially if accompanied by mental status changes.<sup>6</sup> Fluid restriction until the onset of urination is sufficient for managing mild cases with an added clinical benefit observed anecdotally with the oral administration of concentrated salt solutions such as broth. Manifestations of hypotonic encephalopathy, including delirium with psychomotor agitation or sedation, indicate the need for emergent treatment with hypertonic solutions, such as 3% saline or mannitol.<sup>41-43</sup> Such treatment has been associated with decreased mortality and improved outcomes in patients with severe hyponatremia by reducing the neurologic sequelae arising from inadequate management of hypotonic encephalopathy.<sup>44,45</sup> This intervention reduces cerebral edema by reversing the osmotic gradient for the movement of water into the central nervous system without risk for osmotic demyelination syndrome as a secondary consequence, which may arise during the rapid correction of chronic hyponatremia.<sup>46,47</sup> This complication has not been observed during treatment of EAH because the prerequisite compensatory adaptation of brain cells to hyposmolality has not yet taken place. Hypertonic solutions are recommended for optimal emergent treatment of hypotonic encephalopathy under clinical circumstances in which whole-body extracellular fluid volume is expanded, as in EAH, or contracted, as may occur during the treatment of dehydrating illness with reduced osmolarity oral rehydration solutions.<sup>48</sup>

On the basis of the SIADH paradigm, cases of hypotonic encephalopathy were treated with 3% saline at the 2004-2005 Marine Corps and Boston marathons, which resulted in prompt clinical improvement as has also been observed by others.<sup>2,3,6</sup> Infusion of 3% saline at a rate of 1 mL/kg/h rapidly reversed symptoms of acute encephalopathy accompanied by an increase in serum  $[Na^+]$  by 4 to 6 mmol/L during the first few hours (Figure 2). Rapid infusion of a 100-mL bolus of 3% saline may additionally be considered in cases with seizures or coma to prevent respiratory depression from brain stem compression. After reversal of life-threatening neurologic symptoms, the rate of infusion may be adjusted with frequent determinations of serum  $[Na^+]$  to comply with established guidelines for safe maximal rates of correction of hyponatremia during the first 12 to 24 hours.<sup>47</sup> In contrast, infusion of isotonic 0.9% saline may fail to increase the serum  $[Na^+]$  under conditions of SIADH and promote seizures because of progressive cerebral edema.

The mechanisms responsible for nonosmotic stimulation of vasopressin secretion in EAH remain to be determined. Although pain and hypotension, as commonly occur in collapsed marathon runners, are possible factors, release of muscle derived interleukin-6 during rhabdomyolysis may

stimulate secretion of arginine vasopressin, as has been shown to occur in human research subjects.<sup>49,50</sup> Similar to the effects on cortisol and prolactin, stimulation of arginine vasopressin by interleukin-6 may interfere with appropriate physiologic suppression during hypoosmolality. Rhabdomyolysis may be linked to the pathogenesis of EAH, as has been observed in other clinical conditions in which SIADH may accompany inflammatory stress.<sup>50-52</sup> This paradigm provides a unified explanation for the pathogenesis and clinical features of EAH, rather than postulating multiple independent mechanisms.<sup>52</sup>

This report is limited by the small sample size and inherent methodologic constraints associated with observational studies. Collateral pathogenetic mechanisms for EAH, such as salt depletion during ultra-endurance events, deserve study as proposed in a recent analytic model.<sup>53</sup> Hypertonic saline would likely remain the emergent treatment of choice for EAH-induced encephalopathy under such circumstances given the considerations addressed herein.<sup>54</sup> The role of interleukin-6 should be further explored with regard to a genetic predisposition for EAH conferred by single nucleotide polymorphisms of the promoter region, as postulated in other disease states.<sup>55</sup> However, we found no significant correlation between serum interleukin-6 and vasopressin levels in this small sample size.

The efficacy of arginine vasopressin V<sub>2</sub> receptor antagonists as adjunctive treatment for cases of EAH deserves study as these drugs become available.<sup>56</sup> These rapid-onset agents may promote a predictable aquaresis resulting in normalization of serum [Na<sup>+</sup>] in a controlled manner without neurologic injury in EAH, as in other clinical conditions that present with euvolemic hyponatremia.<sup>57-59</sup> Such continued research is likely to further enhance strategies for prevention and treatment of EAH in endurance athletes of all ages and both genders at all levels of ability.

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