UNDERSTANDING EXERCISE-ASSOCIATED HYPONATRAEMIA: FROM PATHOPHYSIOLOGY TO TREATMENT

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ABSTRACT

The practice of extreme sports is becoming more and more common. Despite physiological adaptation, people who intensively exercise are exposed to exercise-associated complications, including hyponatraemia. Exercise-associated hyponatraemia seems to be a consequence of alteration of water regulation, particularly by excessive expression of vasopressin, sodium mobilisation, and interleukin-6 production by muscular cells. Preventing overhydration, both before and during effort, and prohibiting hypotonic solutes during treatment are the leading interventions to correct hyponatraemia.

Keywords: Exercise-associated hyponatraemia, vasopressin, interleukin-6, extreme sports, hypertonic solute.

INTRODUCTION

At the beginning of the 21st century, the practice of extreme sports is becoming more and more common. From half marathons to ultra-trail races, many untrained persons take part in non-professional competitions. Physiologically, the human body is adapted to sustained physical exercise; nonetheless, endurance is a function of many parameters, of which anterior training is a key one. Despite these physiological properties, sportsmen/women are exposed to exercise-associated complications, including rhabdomyolysis malignant hyperthermia, and an unexpected one - hyponatraemia. A growing body of literature is beginning to describe and study the underlying mechanisms explaining the appearance of such a dysnatraemia, as synthesised here.

EPIDEMIOLOGY

Exercise associated hyponatraemia (EAH) is defined as a plasmatic sodium concentration <135 mmol/L within 24 hours following a prolonged physical activity.[1] The first clinical description of this new entity was made in 1985 by Timothy D. Noakes[2] in four athletes after a prolonged effort of >7 hours. From this, a large number of other descriptions appear, beginning with soldiers and very prolonged races. Considering that risk factors for EAH are sustained physical effort, with suboptimal hydration and salt intake, soldiers are of particular importance in the prevention and detection of EAH. Nonetheless, hyperhydration with hypotonic solutes and use of sports drinks are unusual in this context. The recent guidelines about EAH recall to us that prevalence of EAH among US Marine Corps is 20.9/100,000. EAH is considered to be present in about 51% of ultramarathon runners and 18% of ironman triathletes.[3] In an impressive ironman triathlon (3.8 km swim, 180 km cycle, and 42.2 km run), 58 of the 330 finishers had hyponatraemia at the end of the exercise.[4] 31% of the whole group, and 7 out of the 11 severe hyponatraemic runners, were symptomatic.[4] During the Western States (161 km) Endurance Run, 14 out of 47 consenting finishers (30%) had EAH.[3] EAH has more recently been described in other ultra-endurance (defined as distances >42.195 km or 26.218 miles) races. In a very interesting marathon cohort study, hyponatraemia was present in 13% of trained people (median of five previous marathon finishes

on completion of this one) and three persons had a critical hyponatraemia,[5] confirming previous observations in a smaller group of marathon runners.[6] Nonetheless, EAH seems to appear in less serious physical stress. It is probably present in around 16% of hikers or 12% of endurance cyclists.[3] More recently, a Czech study showed an incidence of 5.7% of post-race EAH in ultra-sports participants.[7]

Many factors have been involved in the occurrence of EAH during sustained efforts.[8] Female sex and low body weight (body mass index <20 kg/m^2) are the two major physiological parameters implicated.[5] The increased risk of EAH in high body mass index sportsmen/women is similar to the risk associated with low body mass index. Estradiol and progesterone increase fluid retention and alter sodium regulation during exercise. A study suggests that more fluid is retained and more sodium is lost when estradiol and progesterone are elevated (in case of pregnancy, oral contraceptive taking, or luteal phase of menstrual cycle) in women susceptible to EAH.[9]

Regular workout seems to play a central role; lack of training before a race and being a slow runner (>4 hours for a conventional marathon) are associated with an increased risk of EAH.[5] Exercise behaviour is of paramount importance; excessive drinking during activity is the primary and critical risk factor associated to EAH occurrence. Excessive consumption of water during effort, defined as a consumption of >3 L of fluids during the race or consumption of fluids every mile, correlates with the incidence of EAH.[10] Similarly, weight gain during the race is another risk factor.[10] Of note, this over-drinking behaviour seems to be favoured by sport drinks (enriched solutions with mineral salts and ions, slightly less hypotonic than mineral water) companies, while such drinks do not prevent EAH occurrence.[11,12] Use of non-steroidal anti-inflammatory agents (NSAID) are significantly associated with EAH incidence, probably due to their reduction effect on renal prostaglandin production (and so a decrease in glomerular filtration rate).[5,10]

CLINICAL PATTERNS

A large number of patients remain asymptomatic despite the presence of significant (natraemia <135 mmol/L) and even severe (<130 mmol/L) hyponatraemia.[4,5,8] However, a correlation can be found between deepness and presence of clinical symptoms. In mild forms of symptomatic EAH, specific complaints are usually observed, such as nausea, vomiting, malaise, dizziness, and fatigue.[10] At the opposite end of the clinical and biological pattern, severe signs can be observed. Serious natraemic disorders should recall facing neurological abnormalities: confusion, vigilance disorders, tonic-clonic seizures, or coma reflecting brain swelling. Beside cerebral oedema, neurogenic pulmonary oedema (illustrated by dyspnoea, and potentially leading to acute respiratory failure) can be present.[8] Of paramount importance is the vicious circle which occurs due to the impairment of brain adaptation to osmotic swelling linked to the oxygen deprivation.[13] On the other hand, biological severity is defined by a rapid fall of sodium concentration, with symptoms appearing most frequently when the sodium is <125 mEq/l.[14,15] Whereas hyponatraemia constitutes during the effort, favoured by hypotonic solution intake, symptoms and signs of EAH tend to appear within 30 minutes following the end of the race.

PATHOPHYSIOLOGY

The pathophysiology of EAH is multifactorial: water lost due to increased sweating, modification of antidiuretic hormone (ADH) production in response to exercise, overconsumption of water, and cytokine production in relation to visceral stress. We shall discuss each of these points. For further information, Richard Sterns and Michael Hemmet recently wrote an exhaustive review of these mechanisms.[8]

Perspiration

Due to specific physiological features (shared with camels, donkeys, and horses),[16] humans possess an unusual endurance to prolonged effort and extreme sports, such as marathons or ironmen races. Among particularities allowing such extended efforts, sweating plays a central role by decreasing core temperature in response to evaporation.[16] Thermal regulation finds its origin in the brainstem. Any increase in core temperature always causes a quick and sustained secretory response within a few minutes that leads to temperature normalisation. Despite this very interesting benefit in terms of temperature control, sweating in humans is associated with a high risk of homeostatic alterations. Sweat rate is controlled by body temperature, thus, sweating continues regardless

of the state of hydration of the body. For body temperature varying between 36.8 and 37.8°C, the sweating rate is proportional to the temperature. When sweat rate approaches 30 nl/gland/min, weight loss is 8 kg/hour. Effort level associated with the necessity of such a high sweating flow cannot be maintained for more than 20-30 minutes. On the other hand, a lower intensity effort, associated with a water loss of about 1,800 mL per hour can be prolonged.[10]

During exercise, the metabolic balance of water and mineral salts is broken by massive loss of water and sodium chloride in sweat. >90% of water, and >85% of sodium losses during sport are the result of sweat gland activity.[17] Sweat production depends on primary sweat production (depending on acetylcholine stimulation), corresponding to an isotonic fluid and a secondary partial water reabsorption, ultimately leading to an hypertonic fluid excretion.[18] Mechanisms regulating water reabsorption are still not clear, but cystic fibrosis transmembrane conductance regulator chloride channel and Type 5 aquaporin expression may play a role.[18] Usually linked to aquaporin expression, ADH expression varies during exercise. If ADH expression is increased, sodium sweat concentration rises at the same time; the causality of this link remains unclear. ADH would either be responsible for sweat concentration and increased sweat sodium rate, or would be a normal response to water loss without a direct link with sodium concentration, as suggested by the absence of Type 5 aquaporin expression.[18] On the other hand, a vasopressin concentration seems to correlate with urine sodium concentration, and natriuresis correlates with serum and sweat concentration.

Overconsumption of Water

Of paramount importance is the amount of fluid intake. This was initially described by Timothy Noakes[2] showing a 'water intoxication' hyponatraemia during endurance events in four athletes. In this context of large sodium lost in sweat, mismanagement of hydration due to overconsumption of water during exercise is easily understandable.[19] Interestingly, it was shown more recently that among hyponatraemic patients, the symptomatic ones are the athletes who over-consume water and gain weight during effort.[15,20] This excessive water intake, relative to sodium replacement, will be rapidly aggravated by overhydration and dilutional hyponatraemia[10] and, in a few patients, reduction in water intake was associated with a correction of hydration abnormalities.[2]

Besides the individual perception of thirst leading to an inappropriate absorption of water, guidelines established during the last decade of the 20th century favour this overconsumption by advocating sportspeople to drink large amounts of water, starting the day before the effort and going on from 2 hours before to the whole period of exercise.[21] People were recommended to drink sufficiently to 'replace all the water lost or to consume the maximal amount that can be tolerated'.[21] Minimal sodium intake was suggested, except for effort lasting >1 hour and, in this specific case, sodium addition was excessively low (0.5-0.7g/L). However, the new guidelines corrected this misconception without disappearance of EAH.[22] Nonetheless, hyperhydration during activity on its own cannot summarise hyponatraemia. The kidneys can excrete 750-1,500 mL/hour of water in normal physiological conditions.[23] Dehydration can be assessed directly by body weight measurements before and after exercise.

Another interesting hypothesis is the probable involvement of non-osmotically-active sodium stores[24] in this hyponatraemia. Prolonged exercise in extreme sports participants suffering from EAH seems to lead to a reduced ability to mobilise these sodium stores.

Aldosterone and ADH

ADH, also called vasopressin, is well-known to be produced in response to osmolality increase[25] during health and diseases. Osmotic stimulation of ADH production is a very sensitive system, with a 1-2% modification of plasmatic osmolality leading to a significant modification in plasmatic ADH concentration osmolality.[13,25] Among non-osmotic natural stimuli of ADH production (by hypothalamic paraventricular and supraoptic nuclei) and release by post-pituitary gland are pain, endorphin production, mechanical stresses, temperature elevation, and hypoxaemia.[26]

More recently, copeptin was studied in the occurrence of hyponatraemia during exercise. As expected, similarly to the C-terminal fragment of the ADH, copeptin plasmatic concentrations are correlated to vasopressin during extreme efforts.[27] Interestingly, in a paper studying ultra-marathon race contestants, an increase in both vasopressin and copeptin was observed despite a decrease

in plasmatic sodium concentration.[27] These observations lead to the question of the definition of this vasopressin rise: can it be considered an inappropriate secretion of ADH or a misadaptation of ADH physiological response to overstress due to extreme sports practice?

More recently, cytokine production was shown to be involved in the non-osmotic stimulation of ADH production during effort. Interleukin-6 (IL-6) seems to play a critical role in antidiuresis during sport and inflammation.[28,29] The interconnection between inflammation and neuroendocrine systems is a fascinating illustration of physiological ability to communicate between pathways in the main global aim of homeostasis, despite the absence of certainty about the clinical significance of this recently described mechanism.

IL-6

Prolonged exertion generates an important inflammatory syndrome, compared with that of the sepsis inflammatory response.[30] As previously discussed, IL-6 is involved in a non-osmotic situation of ADH production.[29] On the other hand, haemodilution has been partially related to a systemic inflammatory syndrome secondary to prolonged exercise.[31] Beside their production by inflammatory cells in response to immune stress, cytokines could also be expressed by other cell types such as epithelial or muscular cells, chondrocytes, or osteoblasts. During exercise, IL-6 plasma concentration increased after 30-90 minutes with a peak at the end of the race.[32,33] The more the exercise is sustained, and the more the muscular mass is elevated, the higher the concentration of IL-6.[34,35] Expression of IL-6 is related to muscular production, as a myokine,[33] in response to muscle contraction and reduction in glycogen stockpile. No systemic stimulation of such a myocyte production was observed during physical training. However there is no correlation between myocyte biomarkers and IL-6 production.[34] Beside the effect on ADH production, IL-6 production has a major role in glucose muscular stocks by favouring blood glucose uptake by myocytes in an auto and paracrine way by increasing muscular insulin sensitivity,[36] and mobilisation of glucose liver stocks and hepatic neoglucogenesis through the endocrine pathway.

TREATMENT AND PREVENTION

Considering the frequency of EAH, notably during extreme sports and blinded hyperhydration-associated danger at the acute phase of medical intervention, therapeutics traps, issues, and solutions should be perfectly known by sportspeople and clinicians. Staff at marathons or ironman races should understand the notion of EAH, the gravity of detecting early signs, and the corresponding treatment (Figure 1).[37]

First of all, hyperhydration should absolutely be avoided in this specific population of patients. Similarly, if there is non-symptomatic hyponatraemia, treatment is not necessary.[14] The major quandary is to distinguish EAH from heatstroke and global dehydration. Clinical pattern is usually not helpful, with only a more frequent core temperature elevation and the ordinary absence of respiratory distress during heatstroke and a more severe reduction in diuresis during heatstroke and dehydration than during EAH.[38] Volume of water intake during the race can be sought to help and guide therapeutic intervention. Variation in body weight between the pre and post-effort period can be of singular interest by underlying the absence of weight loss and large amount of water loss in EAH. Nonetheless, natraemia remains the cornerstone of aetiological intervention.

Healthcare of EAH patients can be divided into two periods: the initial one, where hyponatraemia is not available; and the second one, including the confirmation of EAH. During the first one, usually corresponding to the clinical suspicion of symptomatic EAH, following the end of the exercise (from minutes to hours), hypo or isotonic fluid intake must be restricted until the diagnosis is confirmed or excluded.[39] Notably, the transport team must be warned about the risk of intensive hydration with iso or hypotonic fluids.[40] Supportive care should be initiated, notably oxygen therapy in respiratory failure patients, and fluid-filling should be restricted to hypotensive patients, hypotonic solutions being prohibited.

NaCl 3%

Isotonic saline solution is inefficient for the treatment of EAH. Once natraemia is obtained, urine sample has been analysed, and symptomatic EAH is confirmed, treatment involves the administration of a 3% hypertonic saline solution at 1 mL/kg/hour. Sodium intake should subsequently

be adjusted to natraemia evolution. Increases of 1 mmol/L/hour of natraemia during the first 6 hours, 9 mmol/L during the first 24 hours, and 18 mmol/L during the first 48 hours are usually recommended.[41] A more sustained increase (2 mEq/L/hour) is sometimes suggested until symptoms resolve. Athletes of >70 kg (175 lbs)[14] can benefit more from a high rate of sodium administration because of the larger extracellular fluid volume.[15] Ideally, natraemia should not rise to >20–25 mmol/L during the first 48 hours.[42] More recently, the American guidelines of Wilderness Medical Society[39] recommend 100 ml bolus of 3% hypertonic saline, repeated at 10 minute intervals (maximum three times) to increase natraemia from 4-5 mmol/L and reverse cerebral oedema. Of note, when oral intake is possible, oral hypertonic solution can be proposed.[43] However, a comparison of oral or intravenous 3% saline solution in asymptomatic hyponatraemia long-distance runners demonstrated an increase in natraemia in both groups, with no statistical difference; but the raise is far less important in oral intake group.[3] Of note, whereas celerity in natraemia correction is associated with an increased risk in osmotic demyelinisation syndrome occurrence, no such pathology has ever been described in relation with EAH normalisation.

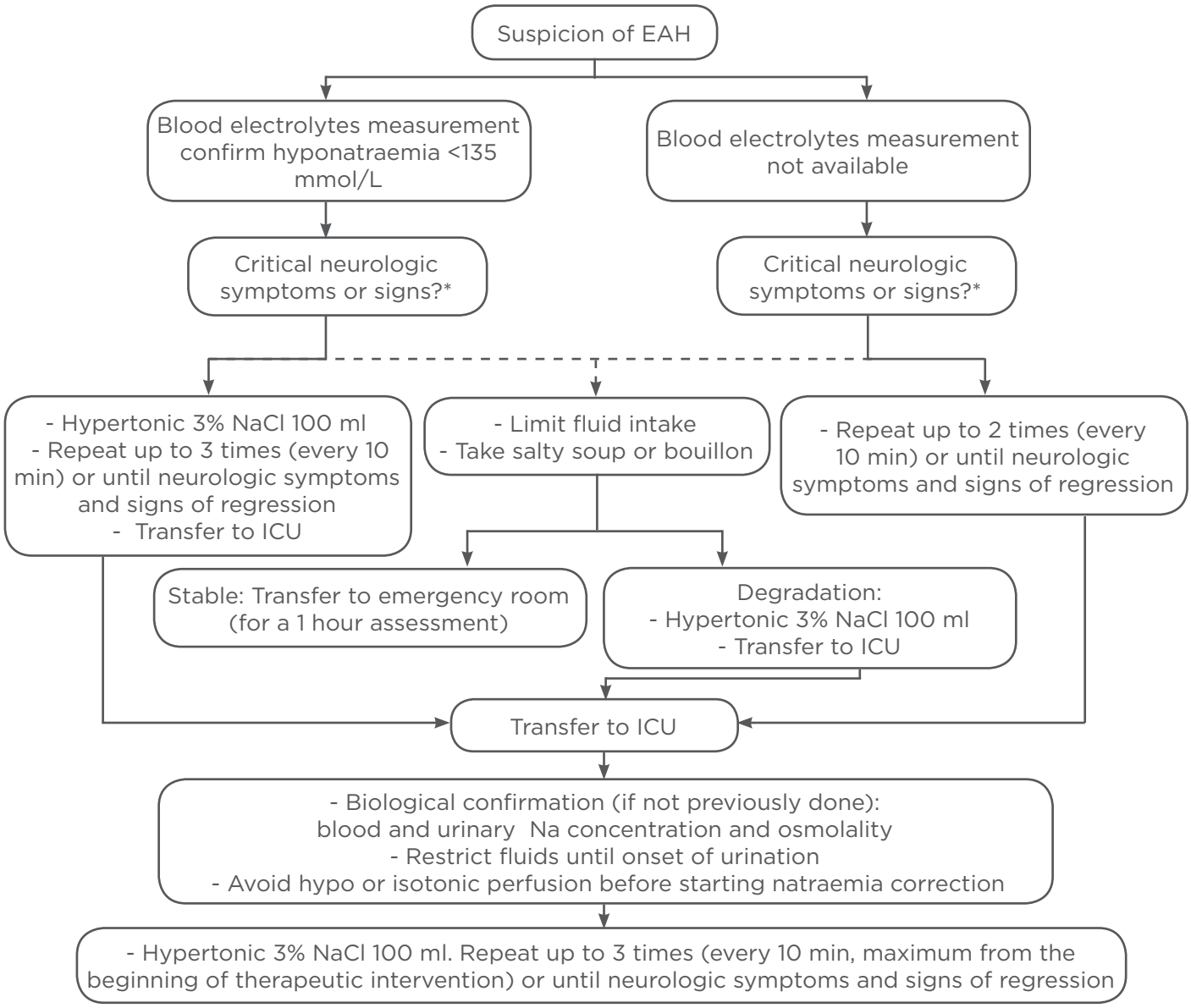

Figure 1: Critical neurologic symptoms or signs - coma or altered mental status, seizures, and severe dyspnoea.

EAH: Exercise associated hyponatraemia; ICU: intensive care unit; NaCl: sodium chloride.

Adapted from International Guidelines.[38]

Vasopressin inhibitors

As hyponatremia is, in EAH, partially due to unsuitable and inappropriate production of vasopressin, use of new antagonists of vasopressin (conivaptan at a dose of 40-80 mg per day) has been suggested. Conivaptan allows an increase in serum sodium from 4-6 mol/L within 12 hours, but is still restricted to hyponatraemia with normal or high volaemic patients.[44] In a recent retrospective study, no differences were observed between hypertonic sodium fluid and conivaptan in terms of natraemia correction. Of interest, none of the treatments were associated with a risk of overcorrection.[45] However, there is currently no guideline for its use in EAH.

Prevention

More importantly than treatment, EAH prevention should be the major concern in this avoidable disease. The monitoring of weight may be an efficient prevention. Prevention consists of monitoring hydration during the exercise and to control water supplies in a range of 400–700 mL hour, depending on body weight and weather conditions. Drinking according to the sensation of thirst is far more appropriate than hyperhydrating oneself in preventing hyponatraemia.[11] Race organisers may reduce the possibility to hydrate (not before 3 km [1.86 miles]).[39] Sodium supplementation does not prevent EAH (during activity <18 hours),[46] and has no effect related to natraemia if the athletes drink according their thirst.[47]

CONCLUSION

EAH is a rare but serious and preventable disease. A wide availability of information for race organisers and people involved in extreme sports is of paramount importance to reduce the incidence of symptomatic hyponatraemia and associated morbidity. Restricting water intake during effort and during the initial phase of medical intervention is the major preventive intervention, and hypertonic sodium solute in symptomatic hyponatraemia patients is the cornerstone therapeutic intervention.

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