Review Article

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Life-threatening hyponatremia in marathon runners: The Varon-Ayus syndrome revisited

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Abstract

Life-threatening hyponatremia can occur when sodium concentration falls to 125 mmol/L or less. Symptoms usually do not depend on the absolute sodium concentration but on the rate of fall. Estimates of mortality in acute hyponatremia are as high as 50%. Marathon runners are at particular risk of developing a syndrome which consists of severe hyponatremia, pulmonary edema and cerebral edema as originally described by Varon and Ayus. This syndrome, if not managed appropriately has a very high morbidity and mortality.

Keywords: Hyponatremia, cerebral edema, hydration, marathon runners, pulmonary edema

Introduction

Endurance sports, such as marathons, every year capture the interest of more participants. Most of these contestants are not professional athletes but recreational runners [1]. In some marathons, many runners collapse, stimulating investigation into physiologic changes and possible health complications during these events. Losses of water and electrolytes have historically been assumed to be the dominant cause of collapse in marathon runners [2].

In recent years, medical attention has focused on the incidence and mechanism of hyponatremia with its attendant pulmonary and neurologic implications in the affected runners. The best strategy to prevent the development of medical emergencies in marathon runners has been the subject of longstanding debate centered on the deal recommendations for fluid intake.

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History

From antiquity until the late 1960s athletes were advised to restrict their fluid intake while exercising [3]. The belief at that time was that fluid ingestion impaired athletic performance [4]. This recommendation changed after 1969, when one publication established the potential dangers of dehydration during exercise [3]. This lead to encouragement of athletes to 'drink as much as possible' while exercising. This premise was based on the following assumptions: First, that fluid loss during exercise must be always replaced; second, that the greatest threat to health during exercise was dehydration; and third that high rates of fluid intake can do no harm [4]. These recommendations decreased the overall prevalence of dehydration during exercise [3].

Years later another medical condition increased its prevalence, threatening athlete's life and causing major morbidity [5]. Noakes and associates in 1985, described hyponatremia as a possible complication during endurance exercise [6]. These authors described the development of hyponatremic encephalopathy during endurance events lasting longer than 7 hours. Between 1989 and 1999 there were 190 cases of water intoxication reported in the US Army, which required hospitalization [7,8]. At least four military recruits died from this condition. These cases leading to a revision of the fluid replacement guidelines in the military in 1999 [9,10].

In order to protect the runners from the effects of over hydration the International Marathon Medical Directors Association (IMMDA) was formed as the Consulting Medical Committee of the Association of International Marathons. IMMDA issued guidelines in order to promote research into the cause and treatment of running injuries. Based on observation and research, they came to the resolution that runners should aim to drink *ad libitum* 400-800mL/hr with the higher rates for the faster, heavier runners competing in warm environment conditions and with lower rates for the slower runners [1,10,11].

Despite these recommendations, in 1999 a cluster of seven life-threatening hyponatremia cases were seen by Varon and Ayus and reported a year later [12]. All of these were critically ill patients that developed hyponatremic encephalopathy after running the Houston marathon. They were all admitted to the hospital and were supported with assisted mechanical ventilation due to severe hypoxemic respiratory failure. Magnetic resonance imaging was performed in six of them showing cerebral edema. This condition was years later recognized as the Varon-Ayus syndrome (VAS) [12].

Exercised-induced hyponatremia

Exercise-induced hyponatremia can be classified into asymptomatic and symptomatic. When there are no symptoms, or they are so mild that do not prompt the athlete to seek for medical care the patient is said to have asymptomatic hyponatremia [5]. In the other hand, with symptomatic hyponatremia, the manifestations can vary, from malaise, nausea, lightheadedness and fatigue to confusion, headache, seizures, coma, and death [13].

Symptomatic hyponatremia has been observed in 0.1-4% of athletes engaged in strenuous exercise and about 9% of collapsed ultra-endurance athletes [14]. Generally, the severity of the symptoms are correlated with serum sodium concentration [15]. Athletes with a concentration below 125 mmol/L are most likely to be symptomatic, and a majority of athletes with serum sodium between 130-134 mmol/L are asymptomatic [15]. Exercise-associated hyponatremia, both symptomatic and asymptomatic, is a common and potentially serious complication of ultra-distance exercise.

Mechanisms of VAS and other types of exercise-induced hyponatremia

Several possible mechanisms have been postulated to lead to exercise- induced hyponatremia and VAS [16]. There are two theories that have been proposed. The first one is related to salt depletion and dehydration and it is based in an anecdotal clinical observation by Hiller and associates, done in the Hawaiian Ironman triathlon where 70% of the athletes treated for hyponatremia were considered to be dehydrated [15]. This statement was done on unspecified clinical grounds and no critical electrolyte measurements were done, so there is no evidence supporting this theory [15]. The second theory, and most accepted because it has shown supportive evidence, is regarding fluid overload. Increase dilute fluid intake and retention plays a large part in the development of hyponatremia [17]. Relevant evidence is the relationship between post-race serum sodium concentrations and the variations in body weight before and after the race. There seems to be an inverse correlation between post-race serum sodium concentrations and body weight changes: the higher increase in weight post-race, the lower serum sodium is expected to be [5,18].

Fluid overload can result from excessive oral intake, encouraged from incorrect guidelines that motivated athletes 'to drink as much as possible', thus leading to fluid accumulation in a physiological third space (intestinal lumen) with subsequent sodium movement into that fluid, or from impaired renal excretion of fluid load [15].

The relationship between mild and asymptomatic hyponatremia (serum sodium values from 130-134 mmol/L) to fluid status is not clearly defined. It is possible that sodium losses may play a role in the development of mild hyponatremia, but there is not enough evidence supporting this [15].

Role of ADH in the development of hyponatremia and VAS

During prolonged exercise, sodium and fluid losses through sweat, lead to a decrease in the extra cellular fluid volume and plasma volume [19]. The need for blood supply to the muscles contributes to a greater reduction in the intravascular volume. As a response to extracellular fluid reduction ADH secretion is stimulated resulting in urinary water retention [19]. Plasma levels of ADH are elevated in virtually all hyponatremic patients [20]. It is possible that the physical stress of endurance exercise results in continued ADH secretion after the cessation of exercise, even when the intracellular fluid volume is expanded and hyponatremia is present. Pain, hypoxia, hypercapnia and hypoglycemia are other stimuli that have been associated with ADH secretion and hyponatremia [21].

Effect of atrial natriuretic peptide

The release of atrial natriuretic peptide (ANP) increases urine sodium loss and its secretion is stimulated by aggressive fluid ingestion during and after exertion [19]. ANP plays an importat role in the regulation of brain water content in several pathologic states characterized by cerebral edema, including hyponatremia [20]. ANP is released by the brain in response to cerebral edema. This was one of the main mechanisms thought to cause VAS [20].

On the other hand, the sodium-potassium ATPase pump is a major determinant of brain adaptation to hyponatremic and hypo-osmolar states [19]. Water moves inside the brain in the presence of a hypo-osmolar plasma in an attempt to maintain osmotic equilibrium. The unmeasured inflow of water can increase intracranial pressure and cerebral edema develops. If there is an inadequate adaptation to this process and brain increases its volume by more than 5-7% brainstem herniation may occur with subsequent death or permanent brain damage [20]. The effect of ANP is to decrease intracellular sodium concentration by the sodium-potassium ATPase pump. It also affects intracranial volume by decreasing the production of cerebrospinal fluid, as an early auto regulation mechanism in cerebral edema [20].

Other Factors

There is evidence that female runners are more prompt to develop hyponatremia, especially severe hyponatremia [19]. In rat models, estrogens decrease the avidity to consume sodium with salt deprivation [22,23]. The sodium ATP-ase pump function was found to be decrease in female rat brains than the male rat brains [20].

It has been postulated that slower runners are more at risk of hyponatremia than faster runners [6,24,25,26]. Slower athletes have more opportunity to drink water, so there is greater chance to be fluid overload [26].

Non-steroidal inflammatory drugs (NSAIDs) have also been postulated to be a potential cause of exercise-associated hyponatremia and in particular the VAS [11,17]. One mechanism by which NSAIDs may affect serum creatinine concentration in athletes is via further depression of glomerular filtration rate. NSAIDs are also spell to potentiate the effect of ADH on the collecting duct and have long been associated with hyponatremia [17,27,28].

Therapeutic suggestions

The management of hyponatremia and the VAS is dictated by the severity of the condition. Cases of patients with asymptomatic hyponatremia usually require no treatment, mostly because these patients do not seek medical attention [5]. In the case an athlete presents with symptomatic hyponatremia, without signs or symptoms of cerebral or pulmonary edema, the management will require several hours of observation and monitoring of serum sodium. There is no clear indication for intravenous fluids administration in these patients, as they are already fluid overloaded [5].

Patients with symptomatic hyponatremia can present with a variety of symptoms that can go from nausea, emesis and weakness to be as dramatic such as respiratory failure with non-cardiogenic pulmonary edema and seizures. These patients must be consider critical and need to be emergently treated monitored in an intensive care unit [5,12]. Treatment with hypertonic saline to create an osmolar gradient of 10-20 mOsm/L to mobilize brain water [29]. Due to the possible danger of brain damage, serum sodium should never be acutely elevated [30]. Brain damage has also been associated with acute excessive changes in serum sodium [30,31]. In authors' experience, serum sodium should never be in normal or above normal levels [31]. The elevation in serum sodium should not be more than 25 mmol/L in 24 hours [30,31]. The main concern when sodium is corrected too fast is the development of central pontine myelinolysis (CPM) that is rare neurological condition that is more common in patients with chronic hyponatremia [32,33,34]. Some authors suggest that 4 molar sodium chloride, 50-60mL injected to a large vein can raise sodium concentration by 7 mmol/L [35]. Following this bolus, an infusion of 3% saline must continue, and increase serum sodium concentration 20-25 mmol/L per 24 hours [36].

Preventive measures for VAS

The mainstay preventive measure is to adopt an adequate fluid replacement regimen during ultra-distance racing in order to avoid overdrinking with a subsequent over fluid state. Fluid intake of 400 –800 ml/hr have been suggested for most athletes [37]. This easily accomplished by reducing the availability of fluids at sports stations. The type of fluid replacement is very important. In the original VAS description, athletes were drinking hypotonic fluid [11,17]. Isotonic fluid ingestion is recommended.

Conclusions

Exercised induced hyponatremia and the VAS are caused by fluid overload, from a high fluid intake. Ath-

letes suffering from symptomatic hyponatremia are at high risk for central nervous damage. A prompt diagnosis and treatment are a must in these cases. The modification in the fluid replacement guidelines will make marathons and other endurance-sport events safer for their participants.

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