CASE REPORT

Considering exercise-associated hyponatraemia as a continuum

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SUMMARY

Exercise-associated hyponatraemia (EAH) always involves a component of overhydration relative to available exchangeable sodium stores. In the majority of cases, this is purely due to excessive consumption of fluids during exercise. In a lesser number of cases, it is apparent that excessive sodium loss through sweat may play a role by decreasing the amount of acutely available exchangeable sodium. Two cases demonstrating the latter, one in an individual with cystic fibrosis (CF) and another in an endurance athlete without CF, demonstrate how elevated dermal sweat losses may contribute to a *relative* dilutional EAH along a pathophysiological continuum.

BACKGROUND

Exercise-associated hyponatraemia (EAH) is a well-described condition where an individual develops low blood sodium associated with physical activity. The most recent EAH Consensus Guidelines define it as hyponatraemia ($[Na^+]$ less than 135 mmol/L) during or up to 24 hours after physical activity.¹ Most clinical scenarios are the result of an excess of total body water (TBW) due to pure overconsumption of hypotonic fluids. Considering that the main determinants of serum $[Na^+]$ are available exchangeable body sodium reservoirs relative to TBW, it is, as some evidence suggests, reasonable to consider that EAH can also develop under conditions of excessive solute loss accompanied by fluid consumption that is in excess relative to a lower available exchangeable sodium reservoir.² Such a situation can easily occur in individuals affected by cystic fibrosis (CF) who are known to lose excess sodium via sweat, placing them at risk for the development of hypovolaemic hyponatraemia after only modest fluid intake.³ We suggest, through the presentation of two cases, that EAH can be viewed as a process occurring along a continuum with pure overhydration in those with normal sweat sodium losses at one end and excessive sodium loss with overhydration relative to immediately available exchangeable sodium in those with high sweat sodium losses at the other end. Two atypical cases of EAH, associated with elevated sweat sodium losses, are presented here: one (Case 1) in a patient with CF during a trip to Haiti in 2016 and another (Case 2) in an amateur triathlete during an Ironman triathlon in 2014.

CASE PRESENTATION**Case 1**

A 26-year-old Caucasian man, diagnosed with CF after an instance of meconium ileus at the age of

3 months, was admitted to the hospital with hypovolaemic hyponatraemia. Hours earlier, he and his wife had been picked up at the airport by the patient's parents who took him directly to the emergency department (ED) because of confusion, exhaustion and uncontrolled emesis. His blood sodium was found to be 116, and he was hospitalised. He and his wife had just returned from a 10-day mission trip to Haiti that involved more strenuous work in the sun and the heat than they had anticipated. His CF phenotype is one considered to be 'classic' with pulmonary disease, pancreatic insufficiency, chronic pansinusitis, malnutrition and vitamin deficiency. He traditionally has taken very good care of his disease with careful compliance to airway clearance, pulmonary treatments, medication regimen, digestive enzymes, vitamins, exercise and body mass index (BMI) maintenance. He had recently graduated from physical therapy school and was employed full-time as a physical therapist. The month prior to the trip, his forced expiratory volume in 1 sec was stable at 69%, BMI was 25.38 (above minimum goal of 23) and chest x-ray was stable with only chronic changes of CF.⁴

The patient reported that he felt as if he had sweat continuously during the trip and that he had 'heat exhaustion.' He felt like he became gradually more fatigued throughout the trip and does not recall feeling thirsty at all. He assumed that he was becoming dehydrated and forced himself to drink water for the entire trip. He tried to eat salty foods and also consumed a commercial sports drink in order to get more salt. Despite being educated by his CF physician prior to the trip to have a salt and fluid intake strategy that did not involve overconsumption of fluids and instead involved drinking to thirst, his lifelong understanding from CF educational resources was that he was more likely to get dehydrated and needed to eat saltier foods and drink beyond his level of thirst. It was to this strategy that he resorted when progressively not feeling well during the trip.

At the time of hospitalisation, the patient's body weight (69.7) was 4 kg less than his pretrip weight (73.7 kg) 1 month prior at the CF clinic, a difference of 5.4%. He had a blood pressure of 138/96 with a heart rate of 97 and was not orthostatic. His respiratory rate was 18, he was afebrile and his oxygen saturation was 96% on room air. He was fatigued and weakened but was coherent and cooperative. His initial blood laboratory data include a sodium of 116 mmol/L, potassium of 3.1 mmol/L, chloride of 70 mmol/L, CO_2 of 31 mmol/L, creatinine of

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0.92 mg/dL and osmolality of 260 mOsm/kg. His urine laboratory data include a sodium of <10 mmol/L and an osmolality of 94 mOsm/kg.

Case 2

A 40-year-old Caucasian woman was admitted to the hospital with EAH, having just completed an Ironman triathlon. Race temperature was in the low 27°C range. She began feeling nausea and confusion within 15 min of finishing the race and was immediately sent to a local ED for evaluation after entering the on-site medical tent. The ED physician stated that the patient was alert but not able to give the entire sequence of events. While in the ED, she had a seizure that was treated with Ativan. Her medical history was positive only for a single negative syncope work-up along with a prior knee and ankle surgery. She was hospitalised for further management.

The patient reported that she had kept herself 'well hydrated with plenty of electrolyte drinks and water' during the race. During her training, she had the experience common to her of being covered in salt after workouts. On race day, she had mechanical issues with her bike and felt that this caused her to expend far more energy during the bike leg of the race than she had intended.

At presentation to the ED, patient's blood pressure was 160/94 with a heart rate of 82. No mention is made of orthostatic changes. Her respiratory rate was 30, she was afebrile and her oxygen saturation was 100% on room air. No weight is recorded in the available hospital records. After her seizure resolved, she is reported to have been alert and cooperative. Her blood laboratory data demonstrated an initial sodium of 116 mmol/L, potassium of 4.0 mmol/L, chloride of 76 mmol/L, CO₂ of 24 mmol/L, creatinine of 1.1 mg/dL and osmolality of 237 mOsm/kg. Her urine laboratory data include a sodium of 12 mmol/L and an osmolality of 107 mOsm/kg.

INVESTIGATIONS

Subsequent to the above cases, sweat was analysed in both cases 1 and 2 by pilocarpine iontophoresis using the Macroduct coils (Wescor, Logan, Utah, USA) for sweat collection and the Wescor Sweat Chek Analyzer (Wescor) for sweat conductivity. Sweat conductivity is demonstrated to reliably correlate with sweat sodium concentration when the Wescor Macroduct system is used with a mean difference of 5 mmol/L between the two. Sweat sodium concentration was, therefore, determined by subtracting 5 mmol/L from the conductivity value.⁵

The individual in case 1 is known to have a sweat chloride of 80 mmol/L from testing completed at the time of his diagnosis of CF. Pilocarpine iontophoresis sweat testing demonstrates a sweat sodium concentration of 127 mmol/L.

After the incident described in case 2, the subject sought sweat sodium analysis through a website. She was mailed a kit that included a sweat patch. Following the instructions included in the kit, she cleaned the area to which the patch was to be applied, applied the patch to her forearm prior to exercise, removed it after 30–40 min and returned it to the laboratory as instructed by mail. The sweat sodium concentration value she received by email was 171 mmol/L. Subsequent pilocarpine iontophoresis sweat testing demonstrated a sweat sodium concentration of 82 mmol/L.

DIFFERENTIAL DIAGNOSIS

Hypovolaemic EAH from overconsumption of fluids relative to immediately available exchangeable sodium in two individuals incurring high sweat sodium losses is our differential diagnosis,

with respect to the most appropriate volaemic classification of EAH.

Case 1 developed subacutely in the setting of repeated days of high sodium loss through sweat with relative overconsumption of fluids accompanying exertion in the heat. The Statement of the third International Exercise-Associated Hyponatremia Consensus Development Conference suggests that individuals with high sodium loss in situations of sustained sweating such as football players during the initial week of training camp are a group that is susceptible to the development of hypovolaemic EAH. Case 1 represents this exact scenario in which subacute and persistent sodium depletion with inadequate replacement results in EAH when accompanied with overconsumption of fluids.¹

To Case 2's knowledge, it has never been suggested that she had CF or needed to be tested for CF. She denied any chronic and recurrent signs and symptoms that would suggest a diagnosis of CF, and denied any family history of CF. Even with complete genome testing for all 2000+ known mutations, CF remains a clinical diagnosis based on a sweat chloride concentration over 60 mmol/L alongside signs and symptoms consistent with the disease.⁶ It is therefore unlikely that case 2 manifests a CF phenotype, but the possibility of being a CF carrier remains untested. However, she reported the regular experience of having dried salt on her clothing after sweating but denied prior episodes of confirmed hyponatraemia. According to the Statement of the third International EAH Consensus, case 2 represents a second category of athlete at risk for hyponatraemic EAH, the Ironman triathlete, especially in hot and/or humid conditions. Case 2 also fits some of the general risk factors for EAH (exercise duration greater than 4 hours, less experience, slower performance pace).¹

TREATMENT

When case 1 arrived at the ED, the treating physician started 0.9% saline intravenously (normal saline (NS)) as a 2 L bolus. The admitting team, however, stopped the NS infusion making the judgement that hyponatraemia had developed in a subacute fashion and that, since the patient was not seizing nor obtunded, would be more appropriately managed with gradual and controlled sodium correction to eliminate the risk of osmotic demyelination syndrome (ODS). Stat laboratory data demonstrated blood sodium to be 127 just 5 hours after the initial 116, and therapy had already been changed to 5% dextrose in water (D5W) at 125 mL/hour with the target goal blood sodium of 126 at 24 hours. DDAVP was administered and sodium was checked at 2-hour intervals. After changing therapies, sodium decreased to 124 over the next few hours and was 125 at hour 24 and 128 at hour 48 at which time D5W was stopped. At the time of discharge on hospital day 3, the patient was asymptomatic and blood sodium was 135 mEq/L. Please refer to [table 1](#) for complete laboratory data.

On arrival in the ED, case 2 was given 1 L of 0.9% saline intravenously. After admission and because of the determination that this was an acute hyponatraemia without risk for ODS, 0.9% saline was changed to 3% saline intravenously in order to more rapidly correct her hyponatraemia. Eleven hours after admission, blood sodium had risen to 125 mmol/L. On the day of discharge, serum sodium at hour 28 was 133 mmol/L and the patient was described as stable and asymptomatic. Please refer to [table 2](#) for complete laboratory data.

Considering current evidence-based guidelines, a discussion of the differences in care between case 1 and case 2 is warranted.¹ Both subjects present with an extracellular volume contraction,

Table 1 Serial laboratory values of plasma [Na⁺] and markers of plasma volume on a case of subacute exertional hyponatraemia in a patient with cystic fibrosis with a sweat [Na⁺] of 127 mmol/L and initial urine [Na⁺] of <10 mmol/L suggesting hypovolaemia

Variable	Admission	Day 1	Day 2
Plasma [Na ⁺] (mmol/L)	116	125	135
Plasma [Cl ⁻] (mmol/L)	70	87	100
Plasma [CO ₂] (mmol/L)	31	29	26
Anion gap	15	9	9
Haematocrit (%)	50.0	42.0	38.3
Haemoglobin (g/dL)	17.4	15	13.7
Total protein (g/dL)	7.5	5.9	5.8
Blood urea nitrogen (mg/dL)	22	21	13

but there are differences in the preferred initial treatment for each case and different than the 0.9% intravenous saline each received on arrival in the ED. While both subjects were in a state of plasma volume contraction, neither demonstrated unstable vital signs. If hypovolaemic shock were a presenting feature, immediate volume expansion is appropriate. Since neither case presented in shock, evidence-based guidelines for the treatment of EAH suggest other preferred initial approaches.¹ In case 1, because of the subacute nature of the development of hyponatraemia over the course of 10 days, the team assuming control of the extended delivery of care was appropriately concerned for the potential of ODS. Due to the lack of neurological sequelae requiring immediate hypertonic saline, we agree that the treatment team appropriately elected to proceed with tight control of the return to normovolaemia and normonatraemia. Current guidelines would allow administration of 100 mL of 3% hypertonic saline to case 1 as the sodium content is not sufficient to raise serum sodium enough to result in ODS and would mainly serve to expand plasma volume.¹ In case 2, however, neurological sequelae in the form of seizure activity was present, making the preferred initial management to be 100 mL of 3% intravenous hypertonic saline with repeated doses (2) at 10 min intervals until clinical improvement.¹

OUTCOME AND FOLLOW-UP

Case 1 resumed normal activity within days of discharge from the hospital. He continues to comply with all CF-related treatments, which includes daily exercise, and is employed full time. He is considering a return to Haiti for more humanitarian work.

Case 2 also resumed regular activities within days of hospital discharge. She is employed full time and has subsequently and

successfully completed triathlons of the half-Ironman distance. Case 2 is considering another attempt at the Ironman distance.

DISCUSSION

EAH became a phenomenon in the 1980s when the sports drink industry blossomed and hydration recommendations transitioned from drinking to thirst to drinking beyond one's thirst in order to prevent dehydration.¹ The severity of EAH can range from asymptomatic to mildly symptomatic (with non-specific symptoms such as nausea and dizziness) to severe EAH with encephalopathy.¹ Since it was initially described, there have been at least 14 reported athlete deaths attributable to EAH and potentially more that have gone unreported.¹ The risk factors for developing EAH are traditionally described as an inexperienced athlete participating in an event of greater than 4 hours duration who advances at a slower pace and overconsumes readily available fluids so that weight gain occurs throughout the duration of exercise. We would like to suggest, with these two cases as examples, that some cases of EAH can be of much greater complexity when high dermal sodium chloride loss is present, accelerating plasma volume contraction and increasing the risk for development of a hypovolaemic variant.⁷ While pure overconsumption of fluids is the far more likely single aetiology in most cases of EAH, there potentially exists a spectrum of development with high sodium loss and relative overconsumption of fluids at the other extreme. As sweat testing has become more easily accessible, it is apparent that more athletes have higher sweat sodium concentrations than has been previously thought and are at higher risk for EAH.⁸ Recent evidence demonstrates ranges from 15 to 99 mmol/L in 44 professional, American football players in one study and 23.2–86.6 mmol/L in 696 professional soccer, rugby, American football, baseball and basketball players.^{9,10} Data are limited on the entirety of genetic versus environmental influences that contribute to dermal sodium losses. However, there is evidence supporting lower availability of the CF membrane conductance regulator (CFTR) chloride channels in otherwise healthy 'salty sweaters' that are not phenotypically different (in terms of sweat sodium output) from CF controls that require further investigation.¹¹

More recently, there appears to be an increase in the recognition and incidence of cases of hypovolaemic hyponatraemia, a condition demonstrated by both cases 1 and 2.¹² Hypochloraemic alkalosis (contraction) has not been studied as a component of hypovolaemic EAH, but it is well known to occur in CF and evidence suggests that hypochloraemia becomes more pronounced as dermal sodium chloride losses increase even in non-CF 'salty sweaters'.⁷ While case 1 is not yet by definition 'alkalotic,' he is very close and may have been in that range within the 24 hours between the end of effort in the heat and presentation to the ER where he was started on NS prior to laboratory work-up. It has not been uncommon for individuals to receive a diagnosis of CF after recurrent episodes of hypovolaemic hyponatraemia with activity. Within the CF population, the process leading to this end-point has been described as 'involuntary dehydration' and has been thought to be due to a lack of thirst response as patients with CF lose exchangeable sodium through a higher concentration of sweat sodium.¹³ More recent evidence indicates that the thirst drive remains intact in patients with CF, most likely favouring protection of hypovolaemia over hypo-osmolality to prevent circulatory embarrassment.⁷ As case 1 demonstrates, the current advice in the CF community that patients with CF drink beyond their thirst in order to avoid dehydration instead risks the development of the hypovolaemic

Table 2 Serial laboratory values of plasma [Na⁺] and markers of plasma volume on a case of acute exertional hyponatraemia in an athlete with a sweat [Na⁺] of 82 mmol/L and initial urine [Na⁺] of 12 mmol/L suggesting hypovolaemia

Variable	Admission	7 hours	24 hours
Plasma [Na ⁺] (mmol/L)	116	121	133
Plasma [Cl ⁻] (mmol/L)	76	87	97
Plasma [CO ₂] (mmol/L)	24	28	30
Anion gap	16	6	6
Haematocrit (%)	43.3	n/a	36.5
Haemoglobin (g/dL)	14.3	n/a	12.7
Total protein (g/dL)	7.7	6.5	6.3
Blood urea nitrogen (mg/dL)	16	12	11

form of EAH. Unless individuals with CF also ingest appropriate amounts of solute, high fluid intake will only function to expand TBW relative to exchangeable sodium similar to the expansion and EAH demonstrated in ultradistance triathletes who overconsume fluids during competition.¹⁴ However, at the present time, evidence-based guidelines for solute and fluid replacement do not exist for the CF population.

Case 2 has an almost identical presentation to case 1 with two exceptions, the acuteness of hyponatraemia and the level of CO₂. The hyponatraemia in case 2 obviously developed more acutely, occurring over the course of a single event on a single day as opposed to multiple contiguous days of activity. Since the risk cut-off for ODS is thought to be hyponatraemia present for longer than 48 hours, duration of hyponatraemia can be an important diagnostic and treatment factor with the more subacute EAH causing confusion and fatigue and the more acute EAH resulting in seizure activity.¹⁵ Current guidelines for the management of EAH are primarily focused around prehospital care, especially when neurological sequelae are present.¹ Once neurological stability is achieved, it is appropriate for treatment to then take place according to the recommendations for acute and subacute hyponatraemia.¹⁵ The second exception is that case 2 has a solidly normal range CO₂. Since case 2's sweat sodium is lower than case 1's, dermal losses of NaCl would be less in comparison with the expectation that it would take a longer duration for a contraction alkalosis to develop when compared with case 1. If case 2 had exerted under the same conditions as case 1, consecutive days of repeated effort in hot and humid conditions, it is our opinion that case 2 would likely move gradually closer to a state of alkalosis.

The accompanying tables provide laboratory data demonstrating that both cases 1 and 2 experienced a drop in haematocrit during hospitalisation and treatment for EAH, suggesting that both were hypovolaemic at the time of presentation and experienced plasma volume expansion during recovery. The key finding between cases 1 and 2 is that they are processing sodium in nearly identical fashion. According to the latest EAH Consensus Statement, clinical confirmation of hypovolaemic EAH is supported by a spot urine sodium concentration of less than 30 mmol/L.¹ In this series, case 1 has a value of <10 mmol/L and case 2 has a value of 12 mmol/L, indications that both are

conserving sodium. Furthermore, both are excreting a dilute urine, indicating that anti-diuretic hormone (ADH) is appropriately suppressed in an effort to release free water. Conservation of sodium and suppressed ADH indicate an appropriate physiological response to restore serum osmolality. Since both have high sweat sodium concentrations, the most plausible explanation in these instances of hypovolaemic EAH is dermal loss of sodium through sweat with overhydration relative to available exchangeable sodium.

Prevention of EAH under the circumstances of high sweat sodium losses is most likely to involve a combination of drink to thirst guidelines alongside an appropriate sodium replacement strategy. To date, evidence-based sodium replacement guidelines have not been developed within either of the endurance athlete or CF communities. Further prospective research to develop sodium replacement guidelines is essential.

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Learning points

- ▶ Exercise-associated hyponatraemia (EAH) probably exists along a continuum.
- ▶ EAH is always due to a component of overhydration relative to the available exchangeable sodium reserves.
- ▶ The higher an individual's sweat sodium concentration, the easier it is to overconsume fluids relative to exchangeable sodium reserves.
- ▶ As sweat sodium concentration increases on the EAH spectrum, the more likely it is that an individual needs sodium replacement along with drinking to thirst to prevent EAH and maintain performance. This is true even for those with cystic fibrosis.
- ▶ The development of evidence-based sodium replacement guidelines is essential during prolonged exercise, especially when held in hot and humid climates.

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