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REVIEW

Postmortem diagnosis of hyponatremia: case report and literature review

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Abstract Hyponatremia is defined as a plasma sodium concentration less than 135 or 130 mEq/L (or mmol/L) and may be responsible for life threatening symptoms that can be observed in a variety of medical conditions. Cases of fatal hyponatremia have been reported in both clinical and forensic literature in situations of water intoxication due to psychogenic polydipsia, amphetamine derivative drug intake, high-endurance exercise, iatrogenic causes, and exceptional cases of child abuse by forced water intoxication. Vitreous sodium levels have been determined to be relatively stable during the early postmortem period and similar to levels found in normal serum of living subjects. Nevertheless, there are relatively few cases of fatal hyponatremia described in literature that underwent exhaustive postmortem biochemical investigations. A case of fatal water intoxication in a psychiatric patient who underwent medicolegal investigations, including postmortem biochemistry, was chosen as a starting point to a literature review of deaths by hyponatremia that may be encountered in the forensic setting.

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Introduction

Hyponatremia, one of the most common electrolyte abnormalities encountered by physicians in the hospital setting, is generally defined as a decrease in plasma sodium concentration to <135 or 130 mEq/L (or mM or mmol/L) [1–4].

In the living, plasma sodium concentration reflects exchangeable total body sodium relative to water content. In the clinical setting, most cases of hyponatremia imply a relative excess of total body water relative to extracellular sodium and can be considered the result of water balance disorders rather than sodium imbalance [4–7].

Hyponatremia may be the cause of mild (and difficult to detect) to life-threatening symptoms that can be observed in a variety of medical conditions. These include congestive heart failure, liver disease, inappropriate antidiuretic hormone syndrome, and medication use (e.g., thiazide diuretics, psychotropic agents, and chemotherapeutic agents) [2, 6].

Both clinical and forensic literature have reported cases of fatal hyponatremia in situations of water intoxication due to psychogenic polydipsia, amphetamine derivative drug intake, high-endurance exercise, iatrogenic causes, and exceptional cases of child abuse by forced water intoxication [8, 9].

Though postmortem assessment of electrolyte imbalances (such as sodium and chloride) is considered difficult to perform for a myriad of reasons, there is a broad consensus regarding the reliability of vitreous sodium levels to estimate antemortem serum sodium concentrations [8–12].

A case of fatal water intoxication in a psychiatric patient who underwent medicolegal investigations was chosen as a starting point to a literature review of deaths by hyponatremia that may

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be encountered in the forensic setting. The results of postmortem biochemical analyses that can support this diagnostic hypothesis were also examined.

Case history

The security staff of the psychiatric unit of a metropolitan prison was warned by two inmates that a third one was convulsing and "vomiting a transparent fluid." Despite rapid medical intervention and resuscitation attempts, the patient did not survive.

The deceased inmate, a 54-year-old Caucasian, tobacco addicted, diabetic, schizophrenic man treated with insulin, paliperidone, aripiprazole, and venlafaxine, was seen compulsively drinking water by two other inmates during the 3 hours preceding his death. The amount of water intake was retrospectively estimated at 5 L.

Macroscopic external examination of the corpse at the death scene revealed the presence of clear, watery vomit on and around the corpse. No blood or wounds were observed at any site. A medicolegal autopsy was ordered by the public prosecutor due to the circumstances of death (death in custody). External examination performed at the medicolegal center (postmortem interval 33 h) did not reveal anything remarkable. Rigor mortis was present in the major and minor joints. Reddish purple postmortem lividity was present on the back and dependent body parts in the supine position and matched corpse position.

At autopsy, the pericardial sac was unremarkable and contained 50 ml of clear fluid. Examination of the pleural cavities showed bilateral effusion (approximately 180 ml on each side). Upper and lower respiratory airways contained a whitish, foamy liquid. The lungs (left lung 800 g, right lung 1150 g) were edematous. On cut section, both edematous lungs exuded frothy pink-white fluid. There was no evidence of a bronchial tumor. The heart weighed 420 g and did not reveal any hypertrophy. The coronary arteries had a normal anatomic course and revealed mild atheromatous disease without significant stenosis. The stomach contained an estimated 200 ml of watery fluid. No identifiable pill components or fragments were found in the stomach contents or upper gastrointestinal tract. The intra-abdominal organs appeared generally wet. The urinary bladder contained 250 ml of pale yellow urine. The spleen, kidneys, and adrenal glands did not show any significant, macroscopic changes. The omentum and small bowel did not show any abnormalities. No other macroscopic changes were noticed elsewhere in the body.

The brain weighed 1430 g and displayed edema with flattening of the gyri and narrowing of the sulci throughout the convexity as well as uncal and mild cerebellar tonsillar grooving. The pituitary gland was normal. The cerebral arteries had a normal anatomic course.

Histological examinations revealed acute generalized visceral congestion as well as cerebral and pulmonary edema. Microscopically, the heart revealed no evidence of contraction band necrosis, subendocardial hemorrhage, or acute myocardial ischemia.

Toxicology (systematic toxicological analysis based on the use of chromatographic techniques and mass spectrometry) revealed the presence of paliperidone, aripiprazole, and venlafaxine within therapeutic blood ranges.

Due to the unavailability of postmortem femoral blood serum samples, biochemical investigations were performed exclusively in the vitreous humor, which was collected 33 h after death. These revealed a sodium concentration of 117 mmol/L and a chloride concentration of 95 mmol/L. Vitreous potassium, urea, ketones, and glucose were all within serum reference ranges. Though lower values of vitreous sodium might be partially explained by the elapsed postmortem interval, the cause of death was given as hyponatremia resulting from acute water intoxication on the basis of the results obtained from all investigations and the absence of pathological findings at autopsy and toxicology.

Discussion

Sodium is the principal osmole, essential for maintaining extracellular fluid volume as well as regulating blood pressure and osmotic equilibrium. Average plasma sodium concentrations are normally 140 mEq/L or 140 mmol/L. Extracellular fluid sodium is maintained by the action of Na^+/K^+-ATPase. Unlike water that freely crosses cell membranes to maintain isotonicity between intracellular and extracellular fluid, sodium cannot freely cross the cell membrane and requires energy-dependent pumps to be transported. Tonicity, or effective osmolality, of a solution refers to its cell shrinking or swelling properties obtained through water loss or gain respectively, by cells therein suspended. The water transfers are driven by differences in osmotic pressure between intracellular and textracellular compartments. Hypertonic solutions cause water exit from cells, hypotonic solutions cause water entry into cells, and isotonic solutions do not cause any net water movement whatsoever [2, 5].

Plasma sodium level is determined by the relationship of exchangeable total body sodium and potassium to total body water. Changes in plasma sodium are typically inversely proportional to total body water. Hyponatremia is defined as a plasma sodium concentration less than 135 or 130 mEq/L (or mmol/L) and may develop following primary sodium deficit, primary potassium deficit, primary water excess, or a combination of these conditions. In most cases, hyponatremia is the result of higher water retention in relation to sodium and potassium with a possible concurrent abnormality in sodium balance [4, 5].

On the basis of plasma osmolality, hyponatremia can be categorized as hypertonic (occurring with an excess of extracellular solutes, other than sodium, that encounter difficulties entering into cells and therefore cause intracellular water to shift into the

extracellular compartment), isotonic (possibly produced following the use of isotonic, non-conductive irrigant solutions, for example during transurethral resection of the prostate, bladder irrigation or laparoscopic, and hysteroscopy procedures in women), or hypotonic. Since sodium is the predominant extracellular osmole, most cases of hyponatremia are hypotonic and can be further classified based on volume status, such as hyponatremia with contracted extracellular fluid volume (hypovolemic-hypotonic hyponatremia), hyponatremia with expanded extracellular fluid volume (hypervolemic-hypotonic hyponatremia), or hyponatremia with normal extracellular fluid volume (euvolemic-hypotonic hyponatremia) [2–5, 13].

Euvolemic-hypotonic hyponatremia is a syndrome feature of inappropriate antidiuretic hormone secretion and increased fluid intake observed in primary psychogenic polydipsia, beer potomania, and amphetamine derivative use. It has also been observed in athletes engaging in high-endurance sports (triathlon, marathon, and iron man events) [5, 14–19].

Though hyponatremia is defined as plasma sodium levels below 135 or 130 mmol/L, symptoms such as lethargy, restlessness, and disorientation generally occur once plasma levels drop to 115–120 mmol/L. Clinical manifestations of hyponatremia are rarely observed unless individuals continue to drink excessive amounts of water (or other fluids) after urine dilution by the kidneys has been maximized and antidiuretic hormone secretion fully suppressed. When compensatory kidney capacity for exaggerated water or fluid intake is exceeded (or in situations of renal dysfunction or reduced renal water excretion), dilutional hypotonic hyperhydration with hyponatremia results [2, 3, 20, 21].

Polydipsia and water intoxication are relatively frequent among schizophrenic patients, particularly in institutional setting. Treatments with lithium or diuretics, as well as the existence of endocrine disorders such as diabetes mellitus, may be causes of polyuria, frequently observed among psychiatric inpatients. In all these polyuric conditions, the primary abnormal mechanism is polyuria with compensatory or "secondary" polydipsia. However, typical, primary, psychogenic polydipsia that induces secondary polyuria may be observed in more than 20% of chronic, psychiatric inpatients. In primary, psychogenic polydipsia, the origin of the water-seeking behavior remains unknown. In almost all cases of polydipsia with water intoxication, there is a combination of polydipsia, impaired free water excretion, and increased release/inappropriate secretion of antidiuretic hormone. Polydipsia in schizophrenic patients is often related to acute positive symptoms, adverse effects of certain neuroleptics (dry mouth or effects resembling inappropriate antidiuretic hormone secretion syndrome), and tobacco dependence (link between nicotine system and inappropriate antidiuretic hormone secretion syndrome). In some polydipsic patients, the kidney fails to excrete all excess fluid. Renal dysfunction is often related to inappropriate antidiuretic hormone secretion syndrome, for which several factors have been involved (psychosis, stress, and the aforementioned adverse effects of certain neuroleptics and tobacco). Alternatively, psychiatric patients without polydipsia may develop a syndrome of inappropriate antidiuretic hormone secretion induced by drugs such as certain neuroleptics, thiazide diuretics, or sulfonylureas. Lastly, hyponatremia in psychiatric patients may further be precipitated by other factors that may decrease free water excretion by the kidneys, such as hypothyroidism [20, 22–31].

Cases of fatal and non-fatal hyponatremia following fluid overconsumption have been frequently described in both clinical and medicolegal literature in recreational amphetamine derivative users, subjects suffering from schizophrenia or anorexia nervosa, individuals receiving simultaneous administration of several psychotropic drugs, athletes, and military recruits (exercise associated hyponatremia) as well as in situations of forced water intake as a form of child abuse. Cases of fatal hyponatremia in healthy individuals with normal renal function have been exceptionally observed following excessive water intake in subjects suffering from common gastroenteritis or simple urinary tract infections. Though cases of non-fatal water intoxication due to perioperative and postoperative excessive fluid infusion, after urologic and gynecologic interventions, or excessive fluid intake over a very short period of time for ultrasonography procedures have been occasionally described in the clinical setting, we found only one forensic case of death caused by iatrogenic water intoxication during gastric lavage [32–75].

Several factors have been postulated to contribute to amphetamine derivative use-associated hyponatremia, including excessive fluid intake in response to central polydipsia, polydipsia as a result of perspiration during rigorous physical activity (e.g., dancing), and perspiration reduction or inhibition. Profuse sweating at a "rave party" can lead to excessive water intake. Up to two liters of perspiration can be lost per hour in a hot environment, especially during intense physical activity such as dancing. If amphetamine derivatives in some way also inhibit perspiration, hyponatremia can occur. One of the main complaints of ecstasy users is dry mouth. Mood-altering drugs such as amphetamine derivatives may also stimulate thirst and cause primary polydipsia irrespective of perspiration or ambient temperature. Moreover, partygoers are usually encouraged to drink large volumes of fluids to avoid dehydration. Inappropriate secretion of antidiuretic hormones following amphetamine derivative use has been also suggested [32, 34, 41–44].

Until recently, the incidence of hyponatremia during endurance exercise (exercise-associated hyponatremia) was unknown and thought to be relatively uncommon. The results obtained from studies performed in the last years have shown that it is not uncommon for endurance athletes to develop hyponatremia at the end of a race, usually in the absence of clear central nervous system symptoms. There have been at

least eight reported deaths from exercise-associated hyponatremia up to 2007. Many of these reports related to a series of fatalities in the military between 1989 and 1996. At least four other deaths have been attributed to exercise-associated hyponatremia in the USA. It is interesting that two of these deaths occurred in doctors [59–67].

Despite the relative wide number of fatal cases of hyponatremia caused by excessive water intake that have been observed in the realm of both the clinical setting and forensic pathology, there have been relatively few cases of fatal hyponatremia described in literature that underwent exhaustive postmortem biochemical investigations (Table 1) [12, 49–53]. This might be due to the fact that most cases of water intoxication (irrespective of the cause) were admitted to hospital before death was formally pronounced, with consequent diagnoses of hyponatremia reached by antemortem laboratory analyses and clinical findings.

On the other hand, numerous reports in forensic literature have evaluated the usefulness of performing sodium determination in vitreous humor for both diagnostic purposes and postmortem interval estimation [9, 11, 76–81].

This could raise the question of whether circumstantial evidence and clinical investigations provide the greatest diagnostic contribution in situations of suspected fatal hyponatremia compared to postmortem biochemical results.

The postmortem changes in vitreous sodium concentrations have been investigated extensively in the past and in recent years in the forensic setting. Though some authors concluded that vitreous sodium levels seem to be relatively stable during the early postmortem period and similar to levels found in normal serum of living subjects, it still remains difficult to affirm that a real consensus actually exist about the predictability of postmortem changes pertaining to vitreous sodium levels in the early postmortem period [9, 81].

Zilg et al. [9] recently demonstrated that postmortem vitreous sodium (and chloride) levels slowly decreased with the postmortem interval (approximately 2.2 mmol/l per day after death), and that postmortem vitreous sodium levels correlated well with antemortem serum sodium levels. According to these authors, the reason for the postmortem decrease in vitreous sodium and chloride concentrations is most probably the diffusion of these electrolytes from the vitreous into the surrounding retinal and choroidal cells, whereas, the potassium diffusion in the opposite direction would be responsible for the postmortem increase in vitreous potassium. Zilg et al. [9] observed, indeed, that comparisons between decreases in vitreous sodium and increases in vitreous potassium lead to constant sums of electrolyte concentrations at any postmortem interval, with vitreous electrolyte concentration possibly occurring at extreme postmortem intervals when very small amounts of vitreous may be found. Based on their results, they emphasized that vitreous sodium levels should always be evaluated together with either the postmortem interval or the vitreous potassium concentration.

Table 1 Summarizes the reported cases of fatal hyponatremia caused by excessive fluid intake that underwent postmortem biochemical investigations. MEq/l or mmol/l have been reported according to the description of the authors of the quoted article

Performed analysis Reported case	Patient characteristics	Vitreous sodium (and chloride) concentration	Serum sodium (and chloride) concentration	Postmortem interval
Farrell and Bower [12]	64-year-old man	92 mmol/l sodium		6 h
	Compulsive water intake			
Chen and Huang [47]	21-year-old female		112 mEq/l sodium (left ventricle serum)	43 h
	Acute iatrogenic water intoxication (gastric lavage)		74 mEq/l chloride (left ventricle serum)	
Radojevic et al. [48]	38-year-old man	112 mmol/l sodium		12 h
	Compulsive water intake			
	Schizophrenia			
Nagasawa et al. [49]	Man in his 20s	111 mEq/l sodium left vitreous	83 mEq/l sodium	4 days
	Compulsive water intake	113 mEq/l sodium right vitreous	55 mEq/l chloride	
	Schizophrenia	83 mEq/l chloride left vitreous 85 mEq/l chloride right vitreous		
Hayashi et al. [50]	69-year-old man		92 mEq/l sodium	2 days
	Compulsive water intake		65 mEq/l chloride	
	Schizophrenia			
DiMaio and DiMaio [51]	54-year-old female	115 mEq/l sodium		Not indicated
	Compulsive water intake	105 mEq/l chloride		

On the other hand, Coe and Apple [82] found significant variation in vitreous sodium values obtained using a variety of instruments and different procedures. According to these authors, the variation in vitreous sodium values between the different procedures might indeed pose real problems in attempting to determine after death the presence of disorders of sodium balance.

Moreover, according to Madea and Lachenmeier [81], before vitreous humor values can be confidently used as a mirror of antemortem serum values, several conceptual problems have to be solved, among others, the distribution of postmortem vitreous values in comparison to serum values in vivo.

Though Chen and Huang [49], Nagasawa et al. [51], and Hayashi et al. [52] reported sodium and chloride concentrations in postmortem serum in three cases of water intoxication, postmortem blood and postmortem serum samples are generally considered unsuitable for sodium determination and, thus, for the postmortem diagnosis of antemortem sodium imbalances [9, 12].

The analysis of the works on this topic found in the forensic literature allows concluding that it is neither advisable nor recommended to attribute the cause of death to disorders of sodium equilibrium exclusively on the basis of vitreous sodium values alone, without the support of complementary data further corroborating this hypothesis. These must include scene investigation elements, morphological findings, and toxicological/biochemical results as well as medical and social histories of the deceased when available. Having said that, the postmortem diagnosis of hyponatremia in situations of water intoxication can be made and partly based on the postmortem biochemical profile of vitreous humor, especially if discriminating values have been calculated after thorough and extensive investigations involving a great number of cases [9, 81].

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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