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REVIEW

Hyponatremia in patients with infectious diseases

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Summary Hyponatremia is a common electrolyte disturbance associated with considerable morbidity and mortality. Hyponatremia may not infrequently be present during the course of an infection, does not cause specific symptoms and may be overlooked by clinicians. Nonetheless, it may reflect the severity of the underlying process. This review focuses on the clinical and pathophysiological aspects of hyponatremia associated with infectious diseases. In the majority of cases, the fall in serum sodium concentration is of multifactorial origin owing to increased secretion of the anti-diuretic hormone either appropriately or inappropriately. Inadvertent administration of fluids may worsen hyponatremia and prolong morbidity.

Introduction

Hyponatremia is the most common electrolyte disturbance in hospitalized patients with an incidence varying considerably (up to 30%) depending on the definition.[1,2] Infectious diseases not infrequently are associated with hyponatremia. Hyponatremia during the course of an infection may be transient and may be overlooked by clinicians since it may not cause specific symptoms. Nonetheless, hyponatremia in the context of infections reflects the severity of the underlying disease, and is associated with prolonged hospitalization and significant morbidity.

In this review, we scrutinize the clinical and pathophysiological aspects of hyponatremia related to infectious disease processes.

Search strategy and selection criteria

Sources included PubMed and EMBASE. Search terms included the combination of 'hyponatremia', 'infection', 'infectious disease', 'syndrome of inappropriate antidiuresis', as well as specific infectious diseases each time. English language papers were reviewed. All articles identified were evaluated, references of retrieved articles were screened, and relevant and representative information was included.

Pathogenesis of hyponatremia

Hyponatremia is caused either by water retention or (less often) by loss of effective solutes (sodium plus potassium) in excess of water.[3] Since the capacity for water excretion may

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be large even under normal conditions, retention of water leading to hyponatremia occurs only in the presence of conditions that impair renal excretion of water. An exception to this rule is primary polydipsia in which the excessive water intake (10–15 L per day) can overwhelm the normal renal excretory capacity.[3,4] Since the suppression of arginine vasopressin (anti-diuretic hormone, ADH) secretion is essential for the excretion of any water load, the presence of inappropriately high serum concentrations of ADH in relation to low plasma osmolality should be considered as the prerequisite for the development and maintenance of hyponatremia. Virtually all the causes of hyponatremia (except for renal failure, primary polydipsia, beer potomania and low dietary solute intake) are characterized by an absolute or relative excess of ADH (despite the presence of hypotonicity) most frequently due to the syndrome of inappropriate ADH secretion (SIADH) or to depletion of effective circulating volume, which is a normal stimulus to ADH secretion.[5,6]

A decrease in serum sodium concentration creates an osmotic gradient between extracellular and intracellular fluid in cells causing movement of water into cells and consequently cellular edema. Cerebral edema explains the majority of the symptoms of hyponatremia that are predominantly neurological. It is worth mentioning that hypoxemia and hypokalemia represent risk factors of neurological complications in hyponatremic patients through acute cerebral edema and osmotic demyelination syndrome, respectively.[7] Consequently, taking into consideration that these conditions are not infrequently observed in patients with infections, they might contribute to adverse outcome in patients with hyponatremia related to infectious diseases.

Hyponatremia due to infections

Hyponatremia is a clinical complication of a wide variety of infectious diseases via several underlying pathophysiological mechanisms (Table 1) discussed below.

Hypertonic hyponatremia: hyponatremia due to infection-induced hyperglycemia

Infections can induce hyperglycemia by increasing the secretion of catecholamines, glucagon, and cortisol. Glucose is an osmotically active substance. Hyperglycemia increases the serum osmolality resulting in movement of water out of the cells and subsequently in a reduction of serum sodium levels by dilution. Therefore, in hyperglycemic patients, the corrected serum sodium concentration [Na^+] should be evaluated, which is calculated by increasing [Na^+] by 1.6 mmol/L for every 100 mg/dL (5.55 mmol/L) increment in the serum glucose above normal; the correction factor 2.4 mmol/L is used when serum glucose concentration is higher than 400 mg/dL (22.2 mmol/L).[8]

It should be also mentioned that uncontrolled diabetes mellitus can also induce hypovolemic-hyponatremia due to osmotic diuresis. Morever, ketone bodies (β-hydroxybutyrate and acetoacetate) obligate urinary electrolyte losses and aggravate the renal Na^+ wasting seen in diabetic ketoacidosis usually precipitated by infections.[9]

Isotonic hyponatremia: hyponatremia due to infection-induced hyperproteinemia

In the context of marked hyperproteinemia and hyperlipidemia, proteins and lipids occupy space in the volume of serum, leading to lower readings in the concentrations of sodium and free water per liter of serum. In fact, the serum sodium concentration, measured per liter of serum, not serum water, is artifactually reduced (pseudohyponatremia). However, the physiologically significant serum water and sodium as well as serum osmolality remain unaffected. Newer methods using ion-selective electrodes in the measurement of serum electrolytes may avoid this problem.[10,11]

Hypergammaglobulinemia due mainly to the polyclonal activation of B-lymphocytes is frequently observed is patients with infective endocarditis, leishmaniasis,

Table 1 Etiologic classification of infection-induced hyponatremia.

Hypertonic hyponatremia (serum osmolality > 295 mosm/kg)
—Infection-induced hyperglycemia
Isotonic hyponatremia (serum osmolality: 280–295 mosm/kg)
—Infection-induced hyperproteinemia (e.g. Leishmaniasis, HCV, HIV)
Hypotonic hyponatremia (serum osmolality < 280 mosm/kg)
1. Hypervolemic hyponatremia
Edematous states:
—Congestive heart failure after viral, bacterial, rickettsial, fungal, or parasitic infection-induced myocarditis
—Hepatic cirrhosis due to HBV, HCV
—Nephrotic syndrome due to poststreptococcal glomerulonephritis, endocarditis, HBV, HCV, HIV, schistosomiasis, filariasis, toxoplasmosis, malaria, syphilis, and mycoplasma
—Advanced renal failure: leptospirosis, hantavirus infections
2. Euvolemic hyponatremia
—SIADH: pulmonary and CNS infections
—Secondary adrenal insufficiency: tuberculosis, malaria, herpes simplex of CNS
3. Hypovolemic hyponatremia
—Exrtarenal salt loss: potentially all infections through diarrhea, vomiting, blood losses or excessive sweating
—Renal salt loss: mineralcorticoid deficiency (tuberculosis, systemic fungal infections, acquired immunodeficiency syndrome mainly due to opportunistic infections), cerebral salt wasting syndrome (tuberculosis)

HCV, hepatitis C virus; HIV, human immunodeficiency virus; HBV, hepatitis B virus, SIADH, syndrome of inappropriate antidiuresis; CNS, central nervous system.