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| RESEARCH ARTICLE

From Gall Bladder Pain to Dilutional Emergency: Cholecystitis-Induced SIADH

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| ABSTRACT

In the setting of severe infections, hyponatremia should not automatically be attributed to dehydration, as intense inflammatory responses can act as powerful neuroendocrine stimuli, triggering a cytokine surge that enhances central ADH release and leads to SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion). If not recognized early, this can result in rapid clinical deterioration. This case illustrates that exact scenario, emphasizing the importance of proper volume assessment and timely measurement of urinary osmolality and sodium. A 65-year-old male presented to our hospital with profound loss of consciousness and a generalized tonic-clonic seizure, secondary to severe hyponatremia in association with clinical and ultrasonographic findings consistent with acute cholecystitis. Through conservative management, including medical stabilization, close monitoring of sodium levels, and initiation of antibiotic therapy, a delayed cholecystectomy was safely performed. The patient remained seizure-free with preserved cognitive function and was discharged in stable condition.

| KEYWORDS

Cholecystitis, Acute Abdomen, Dilutional Hyponatremia, Seizures, SIADH.

| ARTICLE INFORMATION

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1. Introduction

Acute cholecystitis is an acute inflammation of the gallbladder, most often caused by cystic duct obstruction from gallstones [1]. It classically presents in middle-aged patients (often obese women) with sudden onset of right upper quadrant or epigastric pain (sometimes radiating to the shoulder), fever, nausea, and vomiting [1,2]. Murphy's sign is common, and laboratory tests typically show leukocytosis and may reveal mild elevations in liver enzymes or bilirubin if there is biliary obstruction [1]. Acute cholecystitis is extremely common in industrialized countries: up to 10–20% of the population have gallstones, and roughly a third of these will develop acute cholecystitis during their lifetime [1,3]. Risk factors mirror those for gallstones: the "4 F's" – female sex, forties (older age), obesity (or rapid weight loss), and multiparity – as well as certain ethnic groups (e.g., Native Americans) [1]. Diagnosis is largely clinical but supported by imaging. Ultrasound is the first-line test (demonstrating gallstones,

gallbladder wall thickening, pericholecystic fluid, and a positive sonographic Murphy sign) [1]. When ultrasound is equivocal, CT or HIDA (radionuclide) scan may be used for confirmation. Elevated inflammatory markers and characteristic imaging findings establish the diagnosis. If untreated or severe, acute cholecystitis can lead to serious complications. Common local complications include gangrenous cholecystitis, empyema (pus in the gallbladder), and perforation (occurring in up to ~15% of cases) [4]. These can lead to biliary peritonitis or sepsis, and mortality rises substantially once gangrene or perforation occur [4,5]. Other recognized complications are gallstone ileus (from a cholecystoenteric fistula) and emphysematous cholecystitis (gas-forming infection, especially in diabetics) [4]. Biliary sepsis can follow, and pancreatitis or cholangitis may co-occur if stones are impacted in the pancreatic or bile ducts [4]. Notably, severe infection and inflammation can have systemic effects. Intra-abdominal sepsis often causes hyponatremia, and studies have shown that low serum sodium correlates with more severe biliary disease [6]. Indeed, hyponatremia has been observed in gangrenous cholecystitis and other severe infections, likely mediated by stress hormones and cytokines (e.g., interleukin 6) that drive ADH release [7]. Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) is a cause of euvolemic hyponatremia in which excess antidiuretic hormone (ADH) is released relative to body needs. By definition, SIADH presents with hypotonic hyponatremia, inappropriately concentrated urine (urine osmolality >100 mOsm/kg despite hypoosmolality), elevated urinary sodium (on a normal salt diet), and clinical euvolemia (no edema or dehydration) [8]. Patients have normal renal, adrenal, and thyroid function [8]. The pathophysiology is non-osmotic ADH release or action, leading to water retention and dilutional hyponatremia. Classically, SIADH is triggered by CNS or pulmonary pathology, malignancy, or drugs. Common causes include small-cell lung cancer and other tumors (ectopic ADH), pneumonia or tuberculosis, head trauma or stroke, and medications (e.g., SSRIs, anticonvulsants, chemotherapeutics) [9,10]. Infections such as meningitis, encephalitis, or HIV can also incite SIADH via cytokine-mediated ADH release [9,7]. Clinically, SIADH causes symptoms of hyponatremia – nausea, vomiting, headache, confusion, seizures, or coma – depending on severity and rapidity of onset [11]. Diagnostic criteria (Bartter–Schwartz) include serum sodium 100–300 mOsm/kg (often >400), urine sodium >20 mEq/L on a normal diet, and exclusion of renal failure, volume depletion, or other causes [8,12]. Serum uric acid is often low due to renal wasting [12]. Management of SIADH is tailored to severity. In asymptomatic or mild cases, fluid restriction (e.g., 500–1000 mL/day) is first-line [13]. In severe or acute hyponatremia with neurologic symptoms, hypertonic (3%) saline is given to cautiously raise serum sodium and prevent herniation [13]. Other measures include salt tablets, demeclocycline, or vasopressin receptor antagonists (vaptans) in refractory cases [13]. Crucially, underlying causes must be addressed. Rapid overcorrection must be avoided to prevent osmotic demyelination. Although SIADH is most often associated with the lung, brain, or malignancy, any severe inflammatory stress can trigger ADH excess. Infections (especially pneumonia and CNS infections) are well-known precipitants [9,7]. Intra-abdominal infections are less commonly cited, but there is evidence of hyponatremia in intra-abdominal sepsis [6] and acalculous cholecystitis; one report noted that extensive biliary fluid loss (e.g., external drainage) causes ADH-mediated hyponatremia [8]. Cytokines like IL-6 released in severe infection may directly stimulate hypothalamic ADH release [7]. Nevertheless, SIADH triggered by uncomplicated calculous cholecystitis is exceedingly rare. A review of the literature reveals only a handful of related anecdotes: for example, postoperative SIADH after laparoscopic cholecystectomy [14] and in one case after cholecystectomy complicated by Guillain–Barré syndrome [15]. Paraneoplastic SIADH has been documented in gallbladder carcinoma [16], but acute cholecystitis itself has not been recognized as a classic trigger. In short, hyponatremia and SIADH have been noted in severe biliary pathology, yet SIADH as a direct consequence of acute calculous cholecystitis has not been reported in published series. This case is therefore unique and instructive. We describe a middle-aged woman who presented with typical abdominal pain of acute calculous cholecystitis but was found to have profound, symptomatic hyponatremia. Further workup confirmed SIADH as the cause of her dilutional hyponatremia. The coexistence of acute cholecystitis with SIADH posed diagnostic and therapeutic challenges: the symptoms overlapped (nausea, malaise), and fluid management had to balance treating hypovolemia from inflammation against correcting dilutional hyponatremia. Recognizing this rare link – that an intra-abdominal inflammatory process can induce SIADH – is crucial. This case adds to the scant literature and underscores the need to consider SIADH in patients with hyponatremia and acute cholecystitis, as prompt diagnosis and tailored management of both conditions were essential to the patient's recovery.

2. Case Presentation

2.1 Patient's history and Physical Examination

This case study describes a 65-year-old male, a known case of hypertension well-controlled on amlodipine 5 mg daily. He is non-diabetic, does not consume alcohol, and has a body mass index (BMI) of 24. The patient is functionally independent in his daily activities. He was brought to our hospital by his family following a sudden episode of loss of consciousness accompanied by abnormal, jerky movements that lasted approximately ten minutes at home. Two days prior to presentation, the patient began experiencing right upper quadrant abdominal pain. The pain was acute in onset, dull in character, progressively worsening in intensity, and non-radiating. It was associated with reduced appetite and low-grade fever, documented at 37.9°C at home. He did not report urinary symptoms, vomiting, or changes in bowel habits. He had attempted symptomatic relief with oral paracetamol, but this was ineffective. His oral intake subsequently declined significantly, and his family noted increasing confusion and irritability. There were no reported focal neurological deficits at the time. However, during his hospital stay, the patient experienced multiple witnessed episodes of generalized tonic-clonic seizures, each lasting approximately one to two

minutes. He had no prior history of seizures. His medical history was otherwise unremarkable, with no evidence suggestive of heart failure, chronic liver disease, renal impairment, malignancy, head trauma, central nervous system infection, epilepsy, recent changes in medications, or recent surgical interventions. Family history was non-contributory. On physical examination, the patient was drowsy, with a Glasgow Coma Scale (GCS) score of 12 out of 15 (E3, V4, M5). He was afebrile (37.2°C), normotensive (128/84 mmHg), with a heart rate of 88 beats per minute, respiratory rate of 18 breaths per minute, and oxygen saturation of 97% on room air. There were no clinical signs of dehydration. Meningeal signs, including neck rigidity, were absent. Cardiovascular and respiratory system examinations were unremarkable. Abdominal examination revealed localized tenderness in the right upper quadrant, associated with guarding and a positive Murphy's sign. There was no rebound tenderness, palpable masses, ascites, or organomegaly. Neurological assessment showed postictal drowsiness, normal muscle tone, brisk deep tendon reflexes, and no focal neurological deficits.

2.2 Investigations and diagnostic reasoning:

Relevant laboratory investigations, detailed in Table 1, demonstrated profound hyponatremia with a biochemical profile strongly indicative of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), characterized by hypoosmolar plasma, inappropriately elevated urine osmolality, and increased urinary sodium excretion. Point-of-care ultrasonographic assessment of the abdomen revealed a markedly thickened gallbladder wall measuring 5.2 mm, the presence of pericholecystic fluid, and an impacted gallbladder neck, without evidence of common bile duct dilation (5 mm), collectively suggestive of acute calculous cholecystitis. Neuroimaging via non-contrast computed tomography of the brain excluded intracranial pathology, revealing no signs of acute infarction, hemorrhage, or space-occupying lesions, thereby eliminating a central nervous system etiology for SIADH. Additionally, chest radiography showed no pulmonary infiltrates or mediastinal abnormalities to suggest a thoracic cause. The constellation of findings—hypotonic hyponatremia, concentrated urine in the context of hyponatremia, elevated urinary sodium, preserved renal function, and a clinical state of euvolemia—meets the diagnostic criteria for SIADH. The most plausible underlying mechanism is a cytokine-mediated response to acute systemic inflammation secondary to cholecystitis, with elevated levels of interleukins, particularly IL-6 and IL-1β, leading to aberrant stimulation of hypothalamic magnocellular neurons and non-osmotic release of antidiuretic hormone. Furthermore, nausea and visceral pain likely contributed to the potentiation of ADH secretion, exacerbating free water retention, dilutional hyponatremia, cerebral edema, and culminating in seizure activity.

Test	Result	Normal Range
CRP	94	<10
WBC	$13.1x10^9$	$4.0\text{-}11x10^9$\L
Total bilirubin	28	<21 µmol\L
Sodium	112	135-145 mmol\L
Potassium	4.0	3.5-5.0 mmol\L
Creatinine	0.7	0.6-1.1 mg\dL
ALP	160	45-120 U\L
AST	42	<40 U\L
ALT	38	<40 U\L
Serum osmolality	255	275-295 mOsm\kg
Urine osmolality	520	>100 mOsm\kg
Urinary sodium	78	<30 mmol\L

Table 1: results of relevant laboratory investigations.

2.3 Management course

Initial management focused on acute stabilization, with prompt administration of hypertonic 3% sodium chloride solution delivered as two intravenous boluses of 100 mL over 10 minutes each, accompanied by close monitoring of serum sodium levels at 30-minute intervals. The therapeutic objective was to achieve a controlled elevation in serum sodium by approximately 4 to 6 mmol per liter in order to mitigate the risk of osmotic demyelination syndrome. Following this intervention, serum sodium improved from 112 to 117 mmol per liter, coinciding with cessation of seizure activity and restoration of mental clarity. Concurrently, empiric antimicrobial therapy targeting acute cholecystitis was initiated with intravenous ceftriaxone at 2 grams per day and metronidazole 500 milligrams every eight hours. The patient was maintained nil per os and fluid intake was carefully restricted, not exceeding 800 milliliters per day, administered as a slow infusion of isotonic saline. Analgesic management included intravenous paracetamol and adjunctive low-dose opioid therapy. Surgical consultation was obtained, and following interdisciplinary discussion, cholecystectomy was deferred until the patient achieved greater medical stability. Continued correction of hyponatremia was achieved through stringent fluid restriction, with serial sodium levels rising progressively to 119 mmol per liter at 12 hours, 121 at 24 hours, 127 at 48 hours, and 132 at 72 hours. Definitive treatment was accomplished via laparoscopic cholecystectomy performed on day five without complications. Postoperatively, sodium levels stabilized at 137

mmol per liter, and no further seizures were observed. The patient demonstrated preserved cognitive function and was discharged on day eight in a seizure-free state. The resolution of SIADH features following control of the infectious source supports the hypothesis of a transient, inflammation-induced etiology, with no evidence to suggest chronicity of the condition.

3. Discussion

Inflammatory cytokines, particularly interleukin-6 (IL-6), play a pivotal role in the pathophysiology of non-osmotic antidiuretic hormone (ADH) release, a hallmark mechanism underlying the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [8]. Experimental studies have demonstrated that exogenous administration of IL-6 induces a measurable rise in plasma vasopressin concentrations within hours, resulting in a corresponding decline in serum sodium levels [8]. This cytokine-driven, centrally mediated release of ADH bypasses the usual osmotic thresholds that regulate vasopressin secretion, underscoring the significance of inflammation as an independent stimulus [9]. Moreover, additional stressors such as visceral pain and nausea have been shown to amplify ADH release through neuroendocrine pathways, further exacerbating water retention [9]. In clinical practice, this constellation of triggers—cytokine surge, nociceptive stimulation, and emetogenic response—converges most conspicuously in severe infectious states, wherein infection-associated SIADH becomes a well-recognized yet often underappreciated complication [10]. It has been documented in various infectious conditions, including but not limited to community-acquired pneumonia, bacterial meningitis, and acute cholecystitis [2], all of which may provoke a systemic inflammatory response capable of initiating this dysregulation in water balance [2]. From a pathophysiological standpoint, ADH promotes free water reabsorption in the renal collecting ducts via stimulation of V2 receptors, leading to disproportionate water retention in relation to solute excretion [9]. The result is dilutional hyponatremia despite euvolemia or near-euvolemia. A diagnostically significant clue in SIADH is the paradoxical finding of high urinary sodium excretion despite systemic hyponatremia [10]. This occurs as the body attempts to counteract water overload by eliminating sodium, thereby maintaining a relatively normal volume status but at the expense of worsening hyponatremia. This diagnostic signature distinguishes SIADH from hypovolemic causes, where sodium retention is the norm [10]. It is crucial to recognize that rapid or excessive correction of hyponatremia—particularly an increase exceeding 8 to 10 mmol per liter over a 24-hour period—places the patient at risk for osmotic demyelination syndrome (ODS), a rare yet devastating complication characterized by central pontine and extrapontine myelinolysis [11]. Although the incidence of ODS remains under 0.5% in the general population, its associated mortality can approach 50%, and survivors often sustain irreversible neurological deficits [11]. This danger underscores the necessity for judicious use of hypertonic saline, a potentially hazardous intervention that, while life-saving, must be employed with meticulous monitoring [12]. Notably, isotonic saline (0.9% NaCl) may paradoxically exacerbate hyponatremia in SIADH, as the retained water component may exceed the excreted sodium load, further diluting serum sodium concentrations [12]. Pharmacologic agents such as vasopressin V2-receptor antagonists (vaptans) offer a targeted mechanism to counteract the effects of ADH by promoting aquaresis [12]. However, their use is generally discouraged in acute, transient, or reversible forms of SIADH, particularly those triggered by inflammatory insults [11]. In these cases, resolution of the underlying condition—such as bacterial infection—typically leads to normalization of ADH levels without pharmacologic intervention [10]. Moreover, vaptans carry an inherent risk of overly rapid correction, potentially precipitating ODS, especially in patients with severe baseline hyponatremia [11]. Therefore, in transient inflammatory SIADH, fluid restriction and management of the inciting infection remain the cornerstone of therapy [10]. To establish a definitive diagnosis of SIADH, it is imperative to exclude other etiologies of euvolemic hyponatremia. This includes screening for adrenal insufficiency, typically via early morning serum cortisol measurements, and evaluating for hypothyroidism, both of which can mimic the biochemical profile of SIADH [9]. Although this specific case lacked documentation of endocrine exclusion, the temporal relationship between infection onset, inflammatory markers, and rapid improvement following antimicrobial therapy supports an infection-driven mechanism rather than a chronic or endocrine-related cause [10]. In cases of symptomatic hyponatremia, particularly those presenting with neurological manifestations such as seizures or altered mental status, the expected rise in serum sodium following administration of 100 milliliters of 3% hypertonic saline is approximately 1 to 2 mmol per liter [12]. Therefore, repeated boluses must be titrated carefully, guided by both biochemical parameters and clinical response. Importantly, as the inciting inflammatory process resolves, ADH levels may decline precipitously, resulting in abrupt water diuresis and risking an overshoot in serum sodium [11]. This dynamic shift necessitates frequent monitoring—ideally every two to four hours during the acute correction phase—to ensure gradual normalization without crossing safety thresholds [12]. Prompt identification and treatment of SIADH typically lead to full resolution of neurological symptoms [10]. However, in prolonged or mismanaged cases, persistent cerebral edema may culminate in irreversible neuronal damage, underscoring the importance of early intervention [11]. This case reinforces a critical clinical principle: not all hyponatremia occurring in the context of infection is attributable to hypovolemia or dehydration [9]. A high index of suspicion must be maintained, and targeted investigations—particularly urine osmolality and urinary sodium—should be conducted promptly. SIADH may accompany any significant inflammatory or infectious process [10], and failure to recognize its presence can lead to rapid neurological deterioration with potentially grave outcomes [12].

4. Conclusion

It is essential to recognize that not all cases of hyponatremia occurring in the setting of infection should be reflexively attributed to volume depletion or dehydration. Severe infections are potent activators of the neuroendocrine axis, capable of inducing profound physiological responses that extend beyond fluid loss alone. Among these, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a critical yet frequently overlooked entity that may be triggered by systemic inflammation, cytokine release, pain, and associated nausea. When unrecognized or misdiagnosed, SIADH can lead to rapid and potentially life-threatening neurological deterioration, particularly in the context of acute symptomatic hyponatremia. This underscores the necessity of a thorough diagnostic approach, in which targeted laboratory evaluation—especially measurement of urinary osmolality and urinary sodium concentration—plays a pivotal role in differentiating SIADH from hypovolemic states. At the bedside, meticulous clinical assessment of volume status remains the cornerstone of accurate diagnosis. In particular, the identification of a euvolemic patient with marked hyponatremia should prompt serious consideration of SIADH, as true dehydration in such individuals is unlikely. Furthermore, clinicians must be prepared to move beyond so-called "safe" or conservative fluid strategies when the clinical situation demands it. Inappropriate reliance on isotonic saline (0.9% NaCl) in patients with severe hyponatremia and central nervous system manifestations, under the guise of avoiding rapid correction, may paradoxically worsen the condition by promoting further water retention without adequate solute clearance. In such scenarios, hesitation or rigid adherence to overly cautious protocols may inadvertently do harm. Thus, the judicious yet decisive use of hypertonic saline, guided by close biochemical and neurological monitoring, remains an indispensable tool in the acute management of life-threatening hyponatremia, particularly when driven by reversible neuroendocrine dysregulation such as SIADH.

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