AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION (SIADH): ETIOLOGY, PATHOGENESIS, CLINICAL MANIFESTATIONS, DIAGNOSIS, TREATMENT, AND PROPHYLAXIS

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Abstract: Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) is a disorder characterized by excessive release of antidiuretic hormone despite normal or low plasma osmolality, leading to water retention, dilutional hyponatremia, and impaired free-water excretion. Etiologic factors include central nervous system disorders, pulmonary diseases, malignancies—particularly small cell lung carcinoma—various medications, endocrine abnormalities, and idiopathic causes. The pathogenesis involves uncontrolled ADH-mediated activation of renal V2 receptors, resulting in increased aquaporin-2 expression and enhanced water reabsorption. Clinically, SIADH presents with euvolemic hyponatremia manifested by headache, nausea, confusion, seizures, or coma depending on the severity and rate of sodium decline. Diagnosis relies on laboratory findings of low serum osmolality, inappropriately concentrated urine, elevated urine sodium, and exclusion of adrenal, renal, and thyroid dysfunction. Treatment includes fluid restriction, correction of serum sodium with hypertonic saline in severe cases, and use of vasopressin receptor antagonists. Preventive measures focus on early identification of high-risk patients, careful use of ADH-potentiating drugs, and regular electrolyte monitoring. SIADH remains a clinically significant endocrine disorder requiring prompt recognition and controlled management to prevent neurological complications.
Key words: ADH hypersecretion; SIADH; antidiuretic hormone; hyponatremia; euvolemic hyponatremia, vasopressin; V2 receptor.

Introduction

The Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) is a disorder characterized by **excessive release of antidiuretic hormone (ADH, also known as vasopressin)** relative to plasma osmolality, leading to **water retention, dilutional hyponatremia, and impaired free-water excretion**. SIADH is one of the most common causes of euvolemic hyponatremia encountered in clinical practice.

1. Etiology (Causes)

SIADH can result from various **pulmonary, CNS, malignant, pharmacologic, or idiopathic** factors. Major etiologic categories include:

1.1. Central Nervous System Disorders

- Stroke (ischemic or hemorrhagic)
- Traumatic brain injury
- Central nervous system infections (meningitis, encephalitis, brain abscess)
- Brain tumors (primary or metastatic)
- Hydrocephalus
- Guillain–Barré syndrome
- Subdural hematomas

AMERICAN ACADEMIC PUBLISHER
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1.2. Pulmonary Disorders

- Pneumonia (bacterial, viral, fungal)
- Tuberculosis
- Acute respiratory failure
- Asthma exacerbation
- Chronic obstructive pulmonary disease
- Mechanical ventilation with positive pressure
- Pneumothorax

1.3. Malignancies

Certain tumors produce **ectopic ADH**, most notably:

- **Small cell lung carcinoma (SCLC)** – the most classic cause
- Pancreatic carcinoma
- Prostate carcinoma
- Head and neck cancers
- Lymphomas and sarcomas

1.4. Drugs

Numerous medications can stimulate ADH release or potentiate its renal effects:

- SSRIs (fluoxetine, sertraline)
- Carbamazepine, oxcarbazepine
- Cyclophosphamide
- Vincristine, vinblastine
- Chlorpropamide
- MDMA (ecstasy)
- NSAIDs
- Opioids
- Antipsychotics (haloperidol, quetiapine)
- Desmopressin overdose

1.5. Hormonal and Metabolic Disorders

- Hypothyroidism
- Adrenal insufficiency (Addison's disease)
- Severe nausea and pain (potent ADH stimulators)

1.6. Idiopathic

Occurs especially in elderly patients with no identifiable underlying cause.

2. Pathogenesis

SIADH involves **inappropriately high ADH secretion** in the presence of:

- **Low plasma osmolality**, and
- **Normal or increased intravascular volume**.

2.1. Mechanisms of Water Retention

- ADH binds to **V2 receptors** in renal collecting ducts.
- Activates aquaporin-2 channels.
- Increases **free water reabsorption** independently of sodium.
- Result: **dilutional hyponatremia** and decreased serum osmolality.

2.2. Renal and Hormonal Adaptation

- Suppression of the renin–angiotensin–aldosterone system (RAAS)
- Increased natriuretic peptides

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- Increased urinary sodium excretion (natriuresis)
- Maintenance of **euvolemic or slightly hypervolemic** state

2.3. Neurological Consequences

Low serum sodium → water shifts into brain cells → **cerebral edema** → progressive neurologic dysfunction.

3. Clinical Symptoms

The clinical picture depends largely on the **severity and rate of onset of hyponatremia**.

3.1. Mild to Moderate Hyponatremia (Na^+ 125–134 mEq/L)

- Nausea
- Headache
- Anorexia
- Mild confusion
- Muscle cramps
- Fatigue

3.2. Severe Hyponatremia (Na^+ < 125 mEq/L)

- Vomiting
- Agitation
- Disorientation
- Lethargy
- Seizures
- Ataxia
- Coma
- Respiratory arrest (in profound cases)

3.3. Physical Examination

- **Euvolemic appearance**
- No peripheral edema
- Normal blood pressure
- No signs of dehydration

4. Diagnosis

SIADH is a **diagnosis of exclusion**, supported by laboratory findings. Classic diagnostic criteria include:

4.1. Serum Findings

- **Hyponatremia**: Na^+ < 135 mEq/L
- **Low serum osmolality**: < 275 mOsm/kg
- Normal renal, adrenal, and thyroid function

4.2. Urine Findings

- **Inappropriately high urine osmolality** (> 100 mOsm/kg) despite low serum osmolality
- **Increased urine sodium** (> 40 mEq/L)
- Normal urine output or slightly reduced

4.3. Clinical Status

- Euvolemia on physical exam
- Absence of nephrotic syndrome, ascites, congestive heart failure, cirrhosis

4.4. Additional Tests

- Serum cortisol (to rule out adrenal insufficiency)

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- Thyroid-stimulating hormone (TSH)
- CT/MRI brain if CNS pathology is suspected
- Chest X-ray or CT for pulmonary disease or malignancy

5. Treatment

Treatment depends on severity and underlying cause.

5.1. General Principles

- Treat the underlying disorder (infection, tumor, medication-induced causes).
- Correct serum sodium **carefully** to avoid **osmotic demyelination syndrome (ODS)**.
- Rate of correction: **≤ 8 mEq/L per 24 hours**.

5.2. Mild or Asymptomatic Hyponatremia

Fluid Restriction

- First-line therapy
- Restrict fluid intake to **< 800–1000 mL/day**

Enhanced Free-Water Excretion

- Oral **salt tablets**
- Loop diuretics (furosemide) to increase solute-free water excretion

5.3. Moderate to Severe Hyponatremia

Hypertonic Saline (3% NaCl)

Indicated in:

- $Na^+ < 120$ mEq/L
- Seizures
- Severe neurological symptoms

Administer slow infusion with frequent sodium monitoring.

5.4. Vasopressin Receptor Antagonists (Vaptans)

- **Tolvaptan (oral)**
- **Conivaptan (IV)**

Mechanism:

- Block V2 receptors → increase aquaresis

Used in chronic or resistant SIADH.

Monitor liver function with long-term use of tolvaptan.

5.5. Demeclocycline

- Induces nephrogenic diabetes insipidus
- Used rarely due to nephrotoxicity risk
- Alternative for chronic SIADH unresponsive to other measures

6. Prophylaxis (Prevention)

6.1. Identify High-Risk Individuals

- Elderly patients
- Patients on SSRIs, anticonvulsants, or chemotherapy
- Individuals with pulmonary or CNS pathology

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6.2. Preventive Measures

- Avoid or minimize use of ADH-stimulating medications
- Monitor serum sodium regularly in high-risk patients
- Treat underlying diseases (pneumonia, CNS lesions) promptly
- Use caution with hypotonic IV fluids in hospitalized patients
- Educate patients about fluid intake limits when indicated

6.3. Hospital Prevention Strategies

- Prefer **isotonic fluids** for IV maintenance in adults
- Implement electrolyte monitoring protocols
- Early detection through routine hyponatremia screening in postoperative or neurological patients

Conclusion

SIADH is a complex but clinically significant endocrine disorder characterized by inappropriate ADH secretion causing euvolemic hyponatremia. Early identification of etiological factors, combined with precise laboratory diagnosis and careful sodium correction strategies, is essential to prevent neurological complications. Preventive measures and monitoring in high-risk populations contribute significantly to reducing morbidity and recurrence.