SIADH

Introduction

Antidiuretic hormone (ADH) is **arginine vasopressin.**

Ordinarily, release of ADH from the posterior pituitary gland occurs as a physiological response to a drop in plasma volume or an increase in serum osmolality.

The **syndrome of inappropriate antidiuretic hormone (SIADH)** is a form of hyponatremia in which there is an increased level of ADH which is inappropriate to any osmotic or volume stimuli that normally affect ADH secretion.

The syndrome is important for two reasons:

- **Hyponatremia** may cause significant neurological impairment and if severe enough, will be lethal
- It may be a marker of significant **underlying disease.**

SIADH is a **relatively frequent** cause of **hyponatremia**, especially in the elderly.

The diagnosis of SIADH is one largely one of exclusion.

It is principally characterized by an inappropriately concentrated urine in the setting of plasma hypotonicity.

Well defined criteria have been established in order to make the diagnosis.

Treatment can be complex and problematic, but will essentially be guided in the first instance by the severity of the symptoms relating to the hyponatremia.

In the longer term a thorough search for a possible underlying cause needs to be undertaken.

See also separate document on:

- **Hyponatremia (in Renal and Electrolytes folder).**
- **Central pontine myelinolysis (CPM) (in Neurology folder).**

Physiology

Vasopressin is a peptide hormone.

It is derived from a pre-hormone precursor that is synthesized in the hypothalamus and stored in vesicles in the posterior pituitary gland.

It is released from the posterior pituitary gland as a physiological response to a drop in plasma volume or an increase in serum osmolality. It thus helps maintain homeostasis of blood volume and osmolarity.

It primarily acts to increase the permeability to water in the distal convoluted tubules and collecting tubules in the nephrons of kidneys and thus allows water reabsorption and excretion of a smaller volume of concentrated urine, an antidiuresis

Diagnostic Criteria

These are based on blood biochemistry, urine biochemistry, clinical features and the absence of another obvious cause.

1. Blood biochemistry:
    - Hyponatraemia (<130 mmol/L)
    - Hypotonicity (plasma osmolality < 275 mOsm/kg)

      This is measured to rule out pseudohyponatremia.
2. Urine biochemistry:
    - Urine osmolality > 100 mosmol/kg (i.e. inappropriately concentrated)
    - Urine sodium > 30 mmol/L, (with normal dietary salt intake)
3. Clinical euvolemia:

    There should be no clinical signs of *volume depletion* of extracellular fluid such as:
    - Orthostasis.
    - Tachycardia.
    - Decreased skin turgor.
    - Dry mucous membranes.
4. Absence of another obvious cause, in particular there should be:

- **No recent diuretic use.**
- Normal thyroid function.
- Normal adrenal function.

Pathophysiology

Causes of SIADH:

1. Malignant disease:

   This will be largely due to the **ectopic production of ADH** by malignant tissue, in particular:

   - Lung, (**small cell**, mesothelioma).
   - Gastrointestinal, (stomach, duodenum, pancreas).
   - Genitourinary, (ureter, bladder, prostate, endometrium).
   - Lymphomas.
   - Sarcomas.
   - Thymomas.

2. Pulmonary disease:

   - Predominantly infective lung disease.

3. CNS disease:

   - Infection, encephalitis, meningitis, brain abscess, AIDS
   - Brain trauma
   - Stroke, (hemorrhage, infarction, SAH)
   - Brain tumour.

4. Drugs, (excluding diuretic agents):

   A large variety of drugs have the potential to stimulate the release of ADH, or to potentiate its action. Traditionally drugs have been included among the listed causes of SIADH, however some authorities do not include drug causes.

In general terms the groups of agents which most commonly cause SIADH include:

- Cytotoxic agents.
- Psychoactive agents such as antidepressants or antipsychotics.
- Arginine vasopressin analogues, such as desmopressin, oxytocin and vasopressin.

Clinical Features

Important aspects of clinical assessment will include:

1. Symptoms relating to the hyponatremia:

   The predominant symptoms will be those relating to hyponatremia.

   Severity of these symptoms will depend on the **degree of hyponatremia and acuity with which it develops.**

   In general terms:

   Na < 120 mmol/L Symptoms begin to occur below this level:

   - Confusion
   - Agitation
   - Lethargy
   - Weakness
   - Muscle cramps

   Na < 110 mmol/L Symptoms become more severe:

   - Drowsiness
   - Coma
   - Convulsions

2. Euvolemia:

   - The patient should be **euvolemic.** This may be difficult to determine in practice, but nonetheless it is considered an important diagnostic aspect,

because depletion of the effective arterial blood volume stimulates the secretion of arginine vasopressin *appropriately.*

- When expansion of the volume of extracellular fluid is associated with depletion of the effective arterial blood volume (as in cirrhosis), edema is usually evident.

- Detection of extracellular fluid volume deficit clinically can be more problematic than detecting extracellular volume expansion due to edema. In uncertain cases a trial of normal saline can be used, (see treatment section below)

3. General history and examination for evidence of possible malignant disease.

Investigations

See also diagnostic criteria above.

Blood tests:

1. FBE.

2. U&Es/ glucose.

   - Hyponatraemia <130 mmol/L.

3. Plasma osmolality:

   - Plasma osmolality < 275 mOsm/kg

4. TFTs:

5. Consider adrenal function testing:

   - A plasma cortisol may be done to exclude adrenal insufficiency, but corticosteroid administration should not be withheld, pending results if acute adrenal crisis is suspected.

6. Serum ADH levels:

   - These can be done but are not readily available however.

     Levels will be elevated, (despite the presence of hypotonicity and clinical euvolemia).

     Measurement of the serum level of arginine vasopressin is not recommended routinely however, because urinary osmolality levels above

100 mOsm per kilogram of water is usually sufficient to indicate excess of circulating arginine vasopressin. [1]

Urine:

- Urine osmolality.
- Urine sodium.

ECG:

- This is routine for any unwell patient.

CXR:

- This may show evidence of malignant or infective disease.

CT scan:

- Brain, for CNS disease.
- Thorax, abdomen and pelvis, for the presence of occult malignant disease.

Management

Treatment is complex and can be problematic in the first instance.

It will depend on a number of factors including:

1. The degree of hyponatremia
2. The acuity of the hyponatremia, (if known)
3. The symptoms a patient has.
4. The underlying cause of the syndrome, (if known)

The overly rapid correction of a chronic hyponatremia (defined by some authorities as > 48 hours) may lead to the development of central pontine myelinosis, (see also Hyponatremia guidelines). This important consideration must always be balanced against the severity of the symptoms of the hyponatremia.

Each case must be judged on an individual basis, however in general terms the following principles may be followed:

Severe or life threatening symptoms of hyponatremia:

Severe symptoms include **coma and seizures.**

These should be treated with hypertonic saline, (3% saline).

Treatment by rapid correction of is safe when the hyponatremia is acute in onset, (< 48 hours), but if chronic in onset the situation is more problematic, however the benefit in life-threatening encephalopathy clearly outweighs the relatively small risk of central pontine myelinosis.

For dosing details see Hyponatremia document (in Renal and Electrolytes folder).

Mild to moderate symptoms, where the diagnosis is unclear:

When patients have mild to moderate symptoms (confusion/ agitation) and diagnostic uncertainty remains, volume contraction of the extracellular fluid can be ruled out by infusing 2 liters of 0.9% saline over a period of 24 to 48 hours. [1]

Even though 0.9% saline is not the preferred treatment for SIADH, it is usually safe in limited amounts and when the baseline urinary osmolality is less than 500 mOsm per kilogram of water.

Correction of the hyponatremia suggests underlying volume depletion of extracellular fluid, whilst failure to correct it will suggest SIADH.

Chronic asymptomatic:

Asymptomatic patients with **chronic** hyponatremia have a *low risk* of serious neurologic sequelae, but a well documented risk of central pontine myelinosis if this is corrected too quickly.

Treatment therefore should aim to correct the hyponatremia slowly in these cases.

As SIADH is due to inappropriate fluid retention, treatment options will include:

- Adequate solute intake, (of salt and protein)
- **Fluid restriction**
- Pharmacological:
    - ♥ Inhibition of ADH with demeclocycline

Treating the underlying cause:

Ultimately the only definitive way to treat SIADH, will be to treat the underlying cause, if one is found.

Most cases caused by malignant disease will resolve with anti-neoplastic therapy.

Ceasing any offending drug will usually result in resolution.

References

1. Ellison DH, Berl T, The Syndrome of Inappropriate Antidiuresis. NEJM, May 17, 2007. p. 2064-2072.

2. Pasco J. SIADH in Electrolyte Disturbances in, Textbook of Adult Emergency Medicine, Cameron et al 4th ed 2015.

Dr J. Hayes
Reviewed July 2016.