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RESEARCH ARTICLE

A CASE REPORT ON THIAZIDE INDUCED HYPONATREMIA; ADDRESSING AN UNDERESTIMATED COMPLICATION

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Abstract

Hyponatremia is a common and mostly unnoticed electrolyte imbalance in hospitalized patients. Attention and medical management depends on level of depletion below the normal sodium values and presence or absence of symptoms. Drug induced hyponatremia, arising from renal water retention is predominantly attributed to the Syndrome of Inappropriate Diuresis (SIAD). Hyponatremia manifest with signs of escalation in intracranial pressure such as headache, nausea and vomiting, particularly in case of acute onset with significant serum sodium reduction. Urgent medical interference is called for as symptoms ascend to altered consciousness encompassing confusion, drowsiness, seizures and coma. Various drugs such as Argenine Vasopressin Analogue (AVP analogues), Vasopressin Type II (V2) receptor agonist, diuretics, thiazide like agents induce hyponatremia by various mechanisms. Critical in restoring the serum sodium level is the cessation of implicated agent, coupled with the provision of necessary additional support including 3% NaCl, dexamethasone and fluid restriction. Here is a case report of 63 year old female patient with a diagnosis of euvolemic hyponatremia, induced by hydrochlorothiazide. The patient presented with complaints of drowsiness, altered sensorium and 8-10 episodes of vomiting. Laboratory investigation revealed a significant drop of 106 mmol/L in serum sodium, decreased serum chloride and an elevated D- Dimer. The patient was treated in ICU with 3%normal saline, antibiotics and antihypertensive along with prophylactic anticoagulants. Once the patient condition was satisfactory the patient was moved to wards and later discharged.

Introduction:-

Treatment with thiazide diuretics may be most common origin of drug induced hyponatremia. The importance of thiazide induced hyponatremia is reemerging as a result of guidelines recommending thiazides as first line treatment of essential hypertension[3]. Severe acute hyponatremia can give rise to significant complications, emphasizing the importance of precise definition of the hypotonic state associated with hyponatremia for strategic therapeutic planning and mitigating inappropriate management. Hyponatremia can be classified as hypertonic, normotonic or hypotonic in virtue of cause of origin. Hypertonic hyponatremia often have normal total body sodium levels, but a dilutional drop in the serum sodium due to presence of osmotically active molecules in the serum (mannitol or maltose) causing water shift from intracellular to extracellular space. When plasma water fraction falls with an increase in fats and proteins, the measured sodium concentration in the total plasma volume is respectively reduced

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causing normotonic hyponatremia where the plasma water sodium concentration and plasma osmolality are unchanged. Hypotonic hyponatremia points towards the inability of the kidneys to handle excretion of free water to match the intake due to SIAD. Other possible explanations include heart failure and cirrhosis. Classification and diagnosis of hypotonic hyponatremia can be often challenging. Patient Extra Cellular Fluid (ECF) volume is varied in different etiologies. Hypovolemic hyponatremia presents with decreased ECF volume due to loss of body sodium which can be of renal or extra renal in origin and is indicative of volume depletion. Euvolemic hyponatremia presents with a normal ECF volume. The presence of clinically detectable rise in ECF volume is a characteristic feature of hypervolemic hyponatremia which usually results from a disproportionate rise in body water level as a response to sodium excess. The clinical measurement of intravascular volume presents a formidable challenge given its inherent complexity and lack of straightforward assessment methods in routine clinical settings. Hence volume anomalies have to be identified from patient history, laboratory results and physical examinations[6]. Signs and symptoms mostly overlap comprising of vomiting, diarrhea, reduced skin turgor, dry mucous membranes and increased pulse rate. Euvolemic and hypervolemic hyponatremia usually present with additional signs of volume expansion such as subcutaneous edema, pulmonary edema and ascites.

The risk factors of Thiazide Induced Hyponatremia (TIH) are advanced age, female gender, reduced body mass, hypokalemia and concurrent usage of medications impending free water excretion[3]. Mild hyponatremia within the range of 125-132mmol/L typically remains asymptomatic, though subtle manifestations like fatigue may occur. In case of more severe hyponatremia symptoms may include headache, giddiness, lethargy, seizures and coma[1,2]. These presentations in hypertensive induced hyponatremia primarily signify osmotic water shift into brain cells rather than extracellular fluid volume depletion[1]. The most accepted mechanisms of TIH are primary renal, Sodium-Chloride-Cotransporter (NCC) inhibition related and Aquaporin-2 (AQP2) upregulation [1].

Hyponatremia treatment should align with the disease's pathophysiology. In cases of low serum sodium levels, cells either swell or release solutes to maintain equal intracellular and extracellular osmolality. Acutely developing hyponatremia, especially within 48 hours, may lead to dangerous cerebral edema and neurological complications, possibly resulting in brain herniation. Conversely, chronic hyponatremia, evolving over several days, allows brain cells to expel organic solutes, minimizing brain swelling. Consequently, patients with chronic hyponatremia typically experience milder symptoms and are at a lower risk of fatal complications like brain herniation [6]. Most guidelines suggest that 4- 6 mmol/L increase in serum sodium is sufficient to reverse the most dreaded complications of acute hyponatremia [6, 7]. The treatment options other than hypertonic saline (3%NaCl) include the following. Water restriction is effective in early stages of all hyponatremias [6]. Administration of urea in hyponatremic patients is proved effective as it causes rapid resolution of brain edema along with electrolyte free water diuresis [5]. Plasma AVP levels are heightened in over 95% of SIADH cases, making V2R antagonists a targeted approach for its pathophysiology [12]. Conivaptan and tolvaptan, among various studied vaptans, are clinically accessible for treating euvolemic and hypervolemic conditions. Treatment of chronic hyponatremia can be tricky, overly rapid correction of hyponatremia may cause iatrogenic brain damage [6]. Therefore the limits of 25 mmol/L should not be exceeded. Hence it can be summarized that hyponatremia, even though common can be devastating to the patient if underestimated, but can be corrected effectively with a sound knowledge on cause, etiology and treatment.

Case Report

A 63 year old female patient presents to the casualty with complaints of drowsiness, irritability and 8-10 episodes of vomiting from the last 24 hours. On arrival the vitals were stable but the patient was non responsive to oral commands and had altered sensorium. The patient has a known medical history of hypertension and psychiatric illness. For hypertension the patient recently switched to a combination of telmisartan 40 mg and hydrochlorothiazide 12.5 mg once daily, and for psychiatric illness clonazepam 0.25 mg once daily. Imaging studies such as MDCT of brain and 2D echo were performed in the patient and indicated unremarkable findings, where USG abdomen displayed fatty liver. The laboratory investigations revealed a substantial drop in sodium levels, 106mmol/L with urinary sodium above 20. The serum potassium levels were normal but there was a slight decrease in serum chloride level. The TLC count was elevated to 14960cells/ cumm along with increased platelet levels of 6.17lakhs/ cu mm. There was a decrease in lymphocyte to11%. Patient serum urea was on border line at the time of presentation which later dropped to 12.6 mg/dl. Patient had normal serum creatinine, cortisol and thyroid levels. D dimer test exhibited steep increase. The patient was immediately shifted to ICU and was started on isotonic saline and hypertonic saline. The patient developed subcutaneous edema, once after patient condition was noted to deteriorate, isotonic saline was stopped and the patient was placed on hypertonic saline alone. For hypertension the

patient was treated with cilnedipine by withdrawing the culprit drug Telmikind h. The patient was treated with cefuroxime 1gm for infection. Supportive therapy was provided by means of PPI, and anti emetics. Prophylactic anticoagulants were provided in virtue of elevated D-Dimer and other patient factors. 2 amp of inj KCl was provided to support hyponatremia correction. During the treatment patient showed signs of volume depletion such as dry mucous membranes, tachycardia and worsening of sensorium. Once after the patient was hemodynamically stable, she was shifted to the wards and was monitored closely for any complications or recurrence. After 10 days of hospital admission the patient was symptomatically improved and in a satisfactory condition hence discharged. The patient was replaced on tab cilnedipine 5 mg once daily for hypertension. Tolvaptan 15 mg was given for 7 days along with other vitamin supplements and supportive medications. The patient was advised to come for follow-up after 2 weeks.

Discussion:-

The most pronounced risk factors of hyponatremia are advanced age, female gender and concurrent use of medications that lower serum sodium levels. In that context this patient had a predisposed risk of developing hyponatremia. Even though incidence of hyponatremia in patients using Thiazide diuretics is common, a serum sodium decline this steep is rare claiming the significance among other incidents of drug induced hyponatremia. In a case report by Kavya et al [2] hyponatremia is caused by similar use of a combination of ARB with a thiazide diuretic. In a Japanese study[8], different combinations of ARBs and hydrochlorothiazide were analyzed regarding their pattern of causing hyponatremia and it was inferred that the ADR of ARB/ hydrochlorothiazide combination were similar to those of thiazides and therefore concluded that the adverse effects are mainly caused by hydrochlorothiazide and not the ARBs . Another study related to the association between newly initiated thiazide diuretics and hospitalization due to hyponatremia[4], it was evident that thiazide diuretics contributed in one in every four individuals hospitalized for hyponatremia. Thiazides are one among the three drug classes which is a major cause of drug induced hyponatremia which is explained by SIAD. The complaints of this patient overlap with the signs of hypotonic hyponatremia, which includes xerostomia, tachycardia, reduced skin turgor and altered sensorium. In situations of obvious and potentially life-threatening extracellular fluid (ECF) volume depletion, initiation of isotonic fluid resuscitation often precedes routine lab test results. In cases where the initial volume assessment is inconclusive, and both volume depletion and syndrome of inappropriate antidiuretic hormone secretion (SIADH) are potential diagnoses, a fluid challenge serves both diagnostic and therapeutic purposes[6]. For volume depletion, isotonic saline administration leads to increased serum and urine sodium levels after intravascular volume restoration. In SIADH, isotonic saline also raises urine sodium levels, but serum sodium concentration may decrease as the administered sodium is excreted in a concentrated urine volume, and water retention occurs, facilitating the patient condition to worsen as in this case. Inappropriate diagnosis of hyponatremia often leads to illogical therapies and thereby worse clinical outcomes. In this patient euvolemic hyponatremia was confirmed on the basis of complaints on presentation, urine sodium levels, and negative response to isotonic saline. Subcutaneous edema is associated with signs of volume expansion whereas urinary sodium concentration above 20 ascertains the impression of euvolemic hyponatremia. When considering SIADH as a primary diagnosis, especially if significant CNS symptoms are present or the initial serum sodium concentration is below 120 mmol/L, it is advisable to use hypertonic saline (e.g., 3% NaCl) for the initial diagnostic volume challenge to prevent any risk of further lowering serum sodium levels. When potassium is administered to correct intracellular deficits caused by kaliuretic diuretics like thiazides, sodium exits cells. This process increases serum sodium levels even without altering external water balance or introducing additional sodium [6]. Both orally and parenterally administered potassium have a comparable impact on raising serum sodium levels as administered sodium. Patients with Thiazide induced hyponatremia has a high chance of recurrence hence cannot be rechallenged with a thiazide [9]. Regardless of the maneuver or combination of maneuver chosen to correct hyponatremia, vigilant and frequent measurement of serum sodium is desirable to avoid and mitigate overcorrection [6]. Chronic hyponatremia adaptation allows survival, but rapid correction can lead to osmotic demyelination [11]. There are studies suggestive myelinolysis results mostly from overzealous therapy rather than the abnormality itself [6]. This patient did not exhibit signs of improvement proportional to the serum sodium levels. First the patient was symptomatically better followed by increase in serum sodium. This could be due to the resolving of cerebral edema and threats of brain herniation causing neurological symptomatology to subside. When the patient is discharged the choice of whether or not to continue treatment depends on etiology of SIADH, as many causes of hyponatremia are transient and resolve with the treatment of underlying ailments. While considering the benefits of long term vaptan therapy, the economic aspects must be discussed along with possible liver damage to assess the risk to benefit ratio. Upon the absence of a definitive psychiatric diagnosis, the patient was initiated on clonazepam. Once the patient was discharged all the psychotropic medications were withheld for time being.

Conclusion:-

While ARB/Thiazide combinations are widely recognized as cheaper and effective antihypertensive therapies, this case throw light on an alarming incidence of severe hyponatremia caused by such combinations in vulnerable population. This case highlights the need for a standard guideline for the prevention and early recognition of hyponatremia in susceptible patients. The significance of hyponatremia lies in its potential for iatrogenic harm, making accurate diagnosis and treatment imperative. So treatment has to be specific and goal directed.

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