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Critical Insights Of Central Pontine Myelinolysis: Development Of Hypothetical Co-Relation With Hyperparathyroidism, Its Comorbidity

Mr. Vivek Kumar Tiwari[1], K. Akshaya[2]

[1] *M.Pharmacy, Vivek8033@grcp.ac.in, Department of pharmacology, Gokaraju rangaraju college of pharmacy, Bachupally-500090, Hyderabad, India*

[2] *B.Pharmacy, kotagiriakshaya610@gmail.com, Department of pharmacology, Gokaraju rangaraju college of pharmacy, Bachupally-500090, Hyderabad, India*

ABSTRACT

Central Pontine Myelinolysis (CPM) is severe demyelinating disorder traditionally linked to rapid correction of hyponatremia. Recent insights recommend as metabolic and endocrine disturbances may also contribute to its development. This review explores the established comorbidities of CPM — including alcoholism, liver disease, and electrolyte imbalances and proposes a hypothetical correlation with hyperparathyroidism. We suggest that CNS injury-induced stress may elevate cortisol levels, disrupting calcium-phosphate balance and stimulating parathyroid hormone (PTH) secretion. This neuroendocrine-inflammatory cascade could exacerbate osmotic stress on pontine tissue and increased secretion of parathyroid hormone increasing the risk of demyelination and hyperparathyroidsm. Understanding this possible link emphasizes the need for broader metabolic monitoring in patients vulnerable to CPM along with hyperparathyrodism. Further studies are warranted to validate this novel hypothesis and to redefine the systemic approach toward CPM prevention and management.

Keywords: Central Pontine Myelinolysis (CPM), Hyperparathyroidsm, Demyelination, Sodium levels, Calcium levels.

INTRODUCTION

Damage to myelin sheath and nerve cells in pons characterises neurological condition called Central Pontine Myelinolysis (CPM), also known as Osmotic Demyelination Syndrome. This demyelinating condition is acute and does not cause inflammation. After acute correction of chronic hyponatraemia, it often occurs. A symmetric region of myelin disruption in centre of basis pontis is pathological characterisation of CPM. However, similar lesions were observed in other brain regions, including the thalamus, striatum, cerebellar, and neocortical white/gray junctional areas.

Adams et al. initially reported it in their chronic alcoholic patients in 1959. Since then, CPM has been documented in cases of malnourished, excessive blood sugar, liver transplantation, severe burns, anorexia nervosa, and hyperemesis gravidarum. Within a few days of the hyponatremia being quickly corrected, clinical signs of CPM usually start to show. Encephalopathy, coma, and death are just a few examples of the diverse clinical symptoms. Subsequent examples demonstrated correlation with quick sodium correction by 1970s.[1]

HISTORY

1959 - Central pontine myelinolysis was initially described by **Victor and Adams.** There Clinical findings include pseudobulbar paralysis and quadriparesis. Loss of myelin in central pons region is a pathological finding. Malnutrition or alcoholism was the culprit.[1]

1962 - Extrapontine myelinolysis was discovered stating that lesions can also occur outside the pons.

1976 - According to **Tomlinson**, two mid-age females who had no prior history of malnourishment or alcohol abuse and who had hyponatremia were treated with quick salt correction. Rapid changes in awareness, quadriparesis, and dysphagia developed when the sodium was quickly corrected.[2]

1997 - Laureno and Kleinschmidt-DeMasters demonstrated as amount of sodium correction was actually, causative factor using animal models.[3]

1981 - Kleinschmidt-DeMasters and **Norenberg** clearly showed a connection between osmotic demyelination syndrome and quick sodium level adjustments.[4,5]

PREVELANCE

In the general population, there are 250–500 cases of central pontine myelinolysis for every 100,000 people. There are roughly 2500 cases of central pontine myelinolysis for every 100,000 hospitalized patients in the intensive care unit. There are roughly 10,000 cases of central pontine myelinolysis for every 100,000 individuals receiving liver transplants.The mortality rate of central pontine myelinolysis is approximately 12%.

EPIDEMOLOGY

A retrospective study conducted in 2015 found that osmotic demyelination syndrome accounts for 2.5% of all admissions to the ICU. After quick salt correction, 25% of individuals with severe hyponatremic episodes have been shown to experience neurological complications.[6] Patients who have received an orthotopic liver transplant have been found to have a higher incidence of CPM; the majority of these instances occur within 10 days of the transplant.[7] Patients with rapidly improving hyponatraemia levels during the first two days had a higher risk of developing neurological complications. Neurological consequences were not shown to be statistically significantly associated with CPM occurrence when patients were analysed by age, sex, disordered drinking, and the presence of symptoms.[6,8]

CAUSES

A sharp rise in sodium levels is prevalent cause of central pontine myelinolysis. This might occur while treating hypoonatremia, or low sodium levels.
Your body needs sodium as an electrolyte to keep the fluid equilibrium in your cells. Low sodium levels can be brought on by liver disease, excessive alcohol consumption, and a host of other illnesses. Hospitalization and serious sickness may result from untreated hyponatremia. After being admitted to the hospital, medical professionals administer an intravenous (*IV*) sodium solution to treat low sodium levels. When your sodium level rises too quickly, CPM may occur.[5]
Additional reasons for central pontine myelinolysis could be:

- Extended orthotopic liver replacement.
- Hypophosphatemia Secondary to refeeding syndrome.
- Deficiencies in the energy supply and use of neurons and glial cells, which result in glial cell death and consequently, the central pontine myelinolysis clinical syndrome.
- Prolonged ischemia.

SYMPTOMS

Progressive Neurological Symptoms like
Dysphagia
Spastic quadriparesis
Pseudobulbar palsy
Ophthalmoplegia
Locked-in syndrome
Coma
Death

PATHOPHYSIOLOGY

Most prevalent electrolyte anomaly in hospitalized patients is hyponatremia.[9] which is termed as blood sodium concentration ([Na+]) less than 136 mEq/L and is linked to substantial morbidity and mortality .[10]Hyponatremia and the brain have a close and reciprocal relationship; in fact, hyponatremia is often linked to a number of neurological disorders, and hyponatremia itself can have major clinical repercussions that affect the central nervous system . Since hyponatremia affects up to 50% and 38% of patients, respectively, in neurosurgical and neurocritical care settings, it is not unexpected that both conditions are highly common.[11]

Subarachnoid hemorrhage, cerebrovascular accidents, brain tumors, and head trauma are among the common neurological pathologies that cause hyponatremia secondary to either cerebral salt wasting syndrome (CSW) or syndrome of inappropriate secretion of anti-diuretic hormone (SIADH),[12] which are caused by the brain's release of natriuretic peptides or ADH, respectively, in response to an injury. Additionally, a number of medications that affect the nervous system and are commonly prescribed to patients undergoing neurosurgery or neurologic/psychiatric procedures, such as antidepressants and antiepileptic medications, can result in hyponatremia due to SIADH.[10,12,13]

The osmolality of the brain and extracellular fluid are same under healthy conditions.[13] When hyponatremia happens, the osmotic gradient triggers water to migrate into the brain due to the subsequent drop in plasma osmolality, which results in cerebral edema.[14] Astocytes, a type of glial cell which is present in blood-brain barrier and essential for maintaining electrolyte & fluid content of brain's extracellular space, are cells primarily accountable for oedema. [14] Selective enlargement of glial cells in response to hyposmolar stress, whereas sparing neurones, lends credence to idea that astrocytes have localised water channels that protect neurones from water intrusion.[14, 15] Recent research suggests that presence of AQP water channels in glia, particularly AQP1 and AQP4 subtypes, may impact development of cerebral oedema during hyponatraemia.[16] In actuality, water enters glial cells through AQP1 and AQP4 channels when hypoosmolality happens, causing them to selectively expand whereas neurons are largely unaffected.[17] Glial cells aren't the best osmometers, thus you could see an early expansion of the brain. An old conserved homeostatic response that is vital for cell survival is the presence of adaptive mechanisms that prevent brain swelling. This is because changes in cell volume may affect cell activities such as cell-cycle progression, excitement and metabolism.[18] It is well recognised as brain controls the volume of its own cells, and that due to limitations imposed by skull, certain adaptive processes are required to prevent the brain from becoming too big. E arliest adaptive response is the movement of fluid from interstitial space in cerebrospinal fluid and subsequently in systemic circulation. S econd and more permanent adaptation process, "volume regulatory reduction" (VRD), reduces cellular swelling and maintains brain volume balance by extruding intracellular solutes and osmotically needed water.[19] During first 3 hours, the majority of inorganic ions, including Na+, K+, and Cl−, are released by the cells. When the brain swells, Na+-K+ ATPase pump begins to expel Na+ in a manner that is reliant on energy. It prevents cerebral oedema and is the first line of defence. Following this, other ions that are active osmotically are released into cell via channels such volume-sensitive Cl− channel, the K+-Cl− co-transporter, and K+ channels that are dependent or independent of Ca++.[20] An further response involves the expulsion of minute organic osmolytes, including myo-inositol and amino acids, via an osmolyte and anion channel that is purportedly sensitive to volume. Latter is probably a swelling-activated Cl− channel, and it also facilitates extrusion of organic osmotically active solutes. Maintaining organic osmolyte outflow is an important adaptation strategy in conditions of chronic hyponatraemia, and it remains so as long as hyponatraemia persists. Organic osmolytes are responsible for about 35% of the control of brain volume. It should be noted that some of organic osmolytes lost, particularly glutamate, are neuroactive. This means that they can temporarily alter neurological function, leading to symptoms like an increase in seizures and a decrease in the release of excitatory neurotransmitters from synapses. This could explain why people with chronic hyponatremics often have an unstable gait. It is necessary to comprehend mechanism of brain volume control in order to comprehend variety of clinical manifestations of hyponatraemia.

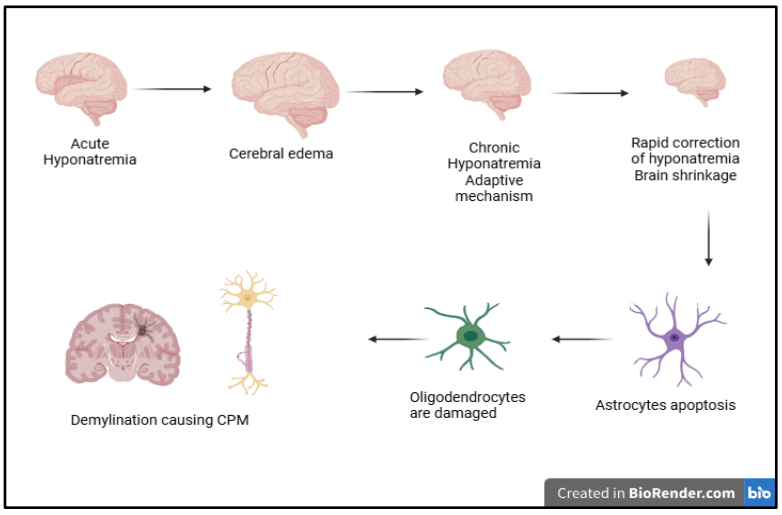

Figure: 1 "Pathophysiological Mechanism of Central Pontine Myelinolysis Following Rapid Correction of Chronic Hyponatremia"

In cases of acute hyponatraemia (less than 48 hours), whenever brain's ability to regulate its volume through electrolyte losses is overwhelmed, brain oedema and severe neurological symptoms, including the risk of death due to brain herniation, can occur. In instances of chronic hyponatraemia, when imbalance persists for more than 48 hours, loss of both organic and electrolyte osmolytes is an especially efficient means of controlling brain volume. Therefore, in chronic hyponatraemia, cerebral oedema decreases and neurological symptoms might be mild or nonexistent. When treating hyponatraemia with active treatment, it is essential to comprehend these complex adaptive processes. The compensatory reactions that hyponatraemia causes are inverted here. To halt fluid loss from cells, it is necessary to recapture organic osmolytes. This might take days since it is so very sluggish. Therefore, an inverse osmotic gradient occurs when the brain's ability to restore lost osmolytes is outstripped by the rate of correction for chronic hyponatraemia. Because of this, brain tissue becomes dehydrated, which may lead to demyelination of white matter.[21]

Pons is most common site of this devastating consequence, known as ODS, which may also harm the brain, basal ganglia, internal capsule, and lateral geniculate body. Additionally, astrocytes play a significant role in development of ODS. Early astrocyte death is a consequence of treating hyponatraemia promptly, according to recent in vitro studies. After astrocytes die, they no longer have the ability to communicate with oligodendrocytes, which is a crucial step in myelination procedure. After astrocytes die, demyelination occurs as a result of inflammatory processes, which include production of pro-inflammatory cytokines & activation of microglia.[22]

DIAGNOSIS

The diagnosis of central pontine myelinolysis (CPM) is based mostly on magnetic resonance imaging (MRI) results and clinical suspicion. Within 24 hours of the beginning of symptoms, MRI, more especially diffusion-weighted imaging (DWI), typically reveals distinctive limited diffusion in the central pons. A "bat-wing" pattern, usually observed later, may be visible in the central pons on T2 and T2-FLAIR imaging.

TREATMENT

Following the onset of CPM, supportive care and symptom management are the mainstays of treatment; there is no known cure.

Primary objective of treating central pontine myelinolysis is to prevent further damage. Many studies have looked at optimal salt adjustment rate. At this time, 8-12 mEq/L of sodium must be adjusted in a 24-hour period. If hyponatraemia persists for more than 48 hours, serum sodium correction rate shouldn't exceed 6-8 mEq/L every 24 hours.

A 3% saline hypertonic solution must be administered when neurologic symptoms are present with severe hyponatraemia (sodium <120 mEq/L). Maintaining a steady sodium level of 8-12 mEq/L every 24 hours by IV fluids should be the primary objective in absence of neurologic signs. While infusing fluids, it is important to monitor serum salt levels every 4-6 hours. If there are noticeable irregularities, it is possible to monitor salt levels every hour.

Retrospective experiments have shown that desmopressin is a safe and effective way to prevent or reverse hyponatraemia overcorrection. These studies compared proactive, reactive, and rescue approaches to desmopressin administration. They found that taking preventative measures by giving desmopressin alongside hypertonic saline reduced the incidence of sodium overcorrection. Usually, 1–2 mcg of desmopressin is injected or applied subcutaneously every 6–8 hours throughout a 24-hour period. At a rate of 15 to 30 milliliters per hour, patients receive intravenous hypertonic saline concurrently.[23,24,25]
Other , treatment stratergies like use of Dexamethasone , Ventilator support, Immunoglobulins, Rehabilitation, Symptom management.

COMORBIDITIES

Central Pontine Myelinolysis (CPM) is often associated with or triggered by other underlying conditions. These are the common comorbidities:

Electrolyte Disorders, Chronic Alcoholism, Liver Disease, Malnutrition, Burns and Trauma, Kidney Disorders, Post-Organ Transplantation, Diabetes Mellitus, **Hyperparathyrodism**, Severe Infections-Sepsis, systemic inflammatory response syndrome (SIRS), Pregnancy, Psychiatric Disorders.

HYPERPARATHYRODISM

Hyperparathyroidism is a prevalent endocrine condition characterised by elevated PTH levels. These levels interfere with normal calcium and phosphorus metabolism. The condition may be caused by either external factors that affect calcium homeostasis or internal factors that lead to increased PTH excretion.

Treatment is necessary for a variety of functional problems induced by hyperparathyroidism, including nephrolithiasis, pathologic bone fractures, neuropsychiatric symptoms, and musculoskeletal complaints. Surgical surgery, particularly parathyroidectomy, is now considered the gold standard for individuals exhibiting symptoms of PHPT or SHPT who have not responded to medicinal therapy. [26]

TYPES OF HYPERPARATHYROIDISM

Primary hyperparathyroidism - Primary hyperparathyroidism is characterised by an overproduction of parathyroid hormone (PTH) due to expansion or development of one or more parathyroid glands. Additionally, they are unresponsive to signals your body sends to them to cease PTH production.[27]

Secondary hyperparathyroidism - When parathyroid glands detect a disease causing elevated phosphate, deficient vitamin D, or low calcium levels, they will produce more parathyroid hormone (PTH) in an effort to raise calcium levels while decreasing phosphate levels. CKD patients are at increased risk.[28]

Tertiary hyperparathyroidism - Chronic, treatment-resistant secondary hyperparathyroidism. The parathyroid glands swell (hyperplasia) and secrete parathyroid hormone (PTH) nonstop.[29]

SYMPTOMS

Kidney Stones (Nephrolithiasis)
Polyuria and Polydipsia
Nephrocalcinosis
Bone Pain and Fragility
Osteoporosis
Osteitis Fibrosa Cystica
Abdominal Pain
Nausea and Vomiting
Constipation
Fatigue and Weakness:
Depression and Anxiety
Cognitive Impairment
Hypertension:
Arrhythmias
Left Ventricular Hypertrophy

PATHOPHYSIOLOGY

Overall, blood calcium levels are raised by hormone PTH, which is critical for maintaining calcium homeostasis. It does this by regulating 3 primary processes.

- Serum's calcium and phosphorus levels are increased due to promotion of bone resorption.
- Lowers calcium excretion in urine via improving calcium absorption in distal convoluted renal tubule & thick ascending loop of Henle.

- Renal proximal tubule contains an enzyme called vitamin D 1-α-hydroxylase, which converts inactive 25-hydroxyvitamin D (25-VitD) in active 1,25-dihydroxyvitamin D (1,25-VitD), thereby enhancing absorption of calcium and phosphorus via gastrointestinal tract.

There is a narrow range of values for the calcium content in extracellular fluid under normal physiological circumstances. Several complex hormonal regulatory mechanisms are required for adequate calcium homeostasis, including PTH, calcitonin, and vitamin D metabolites, which impact calcium transport in the kidneys, bones, and intestines. Calcium absorption in the GI tract occurs via active and passive transport mechanisms. The active transport of calcium is facilitated by 1,25-VitD. No physiological secretion of parathyroid hormone occurs when serum calcium levels are more than 10 mg/dL, while the maximum physiological secretion occurs when serum calcium levels are lower than 7.5 mg/dL.[31]

In response to low calcium levels in the blood, the parathyroid glands release Parathyroid hormone (PTH), which has a balancing effect on the body's skeletal system, renals, and intestines. In the skeleton, PTH suppresses Osteoprotegerin (OPG) and boosts Recptor Activator of Nuclear Factor - Kappa beta Ligand (RANKL) production, which in turn enhances osteoclast activity, promotes bone resorption, and releases calcium into the circulation. PTH causes the kidneys to increase reabsorption of calcium in renal tubules, decrease the reabsorption of phosphate (resulting in excretion of phosphate), and enhance the formation of active vitamin D, also known as calcitriol. The intestinal tract is the next target of active vitamin D, which enhances dietary calcium absorption. The elevated amounts of calcium in the bloodstream are the outcome of several interrelated processes. A negative feedback mechanism prevents the release of more PTH when calcium levels have returned to normal, hence preserving calcium homeostasis.[31,32]

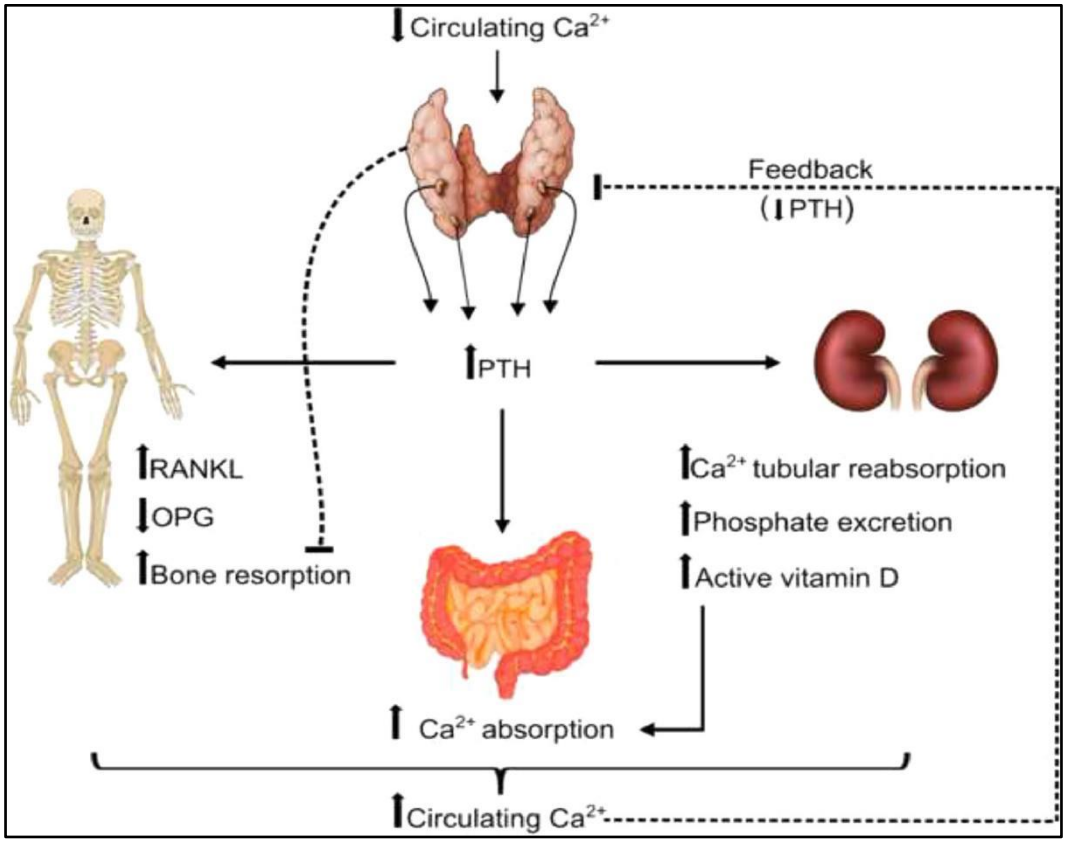

Figure: 2 Role of PTH in Calcium Homeostasis and Bone Resorption [33]

An imbalance between calcium and phosphate occurs in hyperparathyroidism, a disorder characterised by an overproduction of PTH. Bone resorption speeds up, renal calcium reabsorption speeds up, phosphate reabsorption speeds down, and intestinal calcium absorption speeds up thanks to vitamin D activation, all because of elevated PTH. Hypercalcemia and hypophosphatemia are the outcomes of this process. Secondary hyperparathyroidism develops when calcium levels are too low as a result of chronic renal illness or a lack of vitamin D, whereas primary hyperparathyroidism is often caused by a parathyroid adenoma, hyperplasia, or

carcinoma. If secondary hyperparathyroidism continues untreated, it might develop into tertiary hyperparathyroidism. Weakened bones, renal stones, and systemic problems are all part of the cumulative impact.[34]

DIAGNOSIS

The diagnosis of hyperparathyroidism typically begins with blood tests showing elevated serum calcium levels (hypercalcemia). This is confirmed by measuring parathyroid hormone (PTH) levels, which are inappropriately elevated or at the high end of normal despite high calcium, indicating primary hyperparathyroidism. Other supportive lab findings include low serum phosphate, high or normal alkaline phosphatase, and increased urinary calcium excretion. Secondary hyperparathyroidism occurs when parathyroid hormone levels are high despite normal or low calcium levels. This condition is often caused by chronic renal disease or a lack of vitamin D. Imaging studies like neck ultrasound, sestamibi scan, or 4D-CT scans may be used to localize abnormal parathyroid glands before surgery. Bone mineral density tests Dual-Energy X- ray Absorptionmetry (DEXA scan) and renal imaging (to detect kidney stones) are also important in assessing complications of the disease.[35]

TREATMENT

The intensity and kind of hyperparathyroidism dictate course of therapy. Surgical excision of the hyperactive parathyroid gland(s) is gold standard for treating primary hyperparathyroidism. This is particularly true for individuals who are experiencing symptoms or who have developed consequences such as osteoporosis, kidney stones, or abnormally high calcium levels. Thorough surveillance with routine blood tests, bone density scans, and kidney assessments could be suitable for moderate, asymptomatic instances. In cases when surgery is not an option, medications such as bisphosphonates or calcimimetics may be utilised to safeguard bone density or reduce calcium levels, respectively. Supplemental vitamin D, phosphate binders, and management of chronic renal illness are examples of treatments that aim to address the underlying cause of secondary hyperparathyroidism. If the glands grow autonomously hyperactive, surgical intervention may be necessary for tertiary hyperparathyroidism, which usually occurs after long-term secondary hyperparathyroidism. Important components of management include lifestyle changes such as drinking plenty of water, limiting calcium consumption, and continuing to exercise regularly.[36,37]

HYPOTHETICAL CORELATION BETWEEN CPM AND HYPERPARATHYRODISM

After demylination in CPM injures the central nervous system (CNS), a series of neuroendocrine and inflammatory reactions are set in motion, with the Hypothlamic- pitutiary- adrenal axis (HPA) playing a pivotal role.[38,39,40] Hypothalamus is stimulated to emit Corticotropin-releasing hormone (CRH) & Arginine Vasopressin (AVP) when neuronal and glial injury causes the production of pro-inflammatory cytokines such interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α). Adrenocorticotropic hormone (ACTH) is released from the anterior pituitary gland as a result of this activation, which in turn increases the production of cortisol from the adrenal cortex.[41] Cortisol, the principal stress hormone, exerts profound effects on calcium metabolism by reducing intestinal calcium absorption, enhancing renal calcium excretion, and promoting bone resorption. These actions collectively predispose the individual to hypocalcemia. In response, the parathyroid glands are stimulated to secrete parathyroid hormone (PTH) in an attempt to restore calcium homeostasis. Prolonged stress and persistent hypocalcemia can result in secondary hyperparathyroidism. Thus, CNS injury sustained cortisol excess, linking neurotrauma to potential endocrine complications.[42]

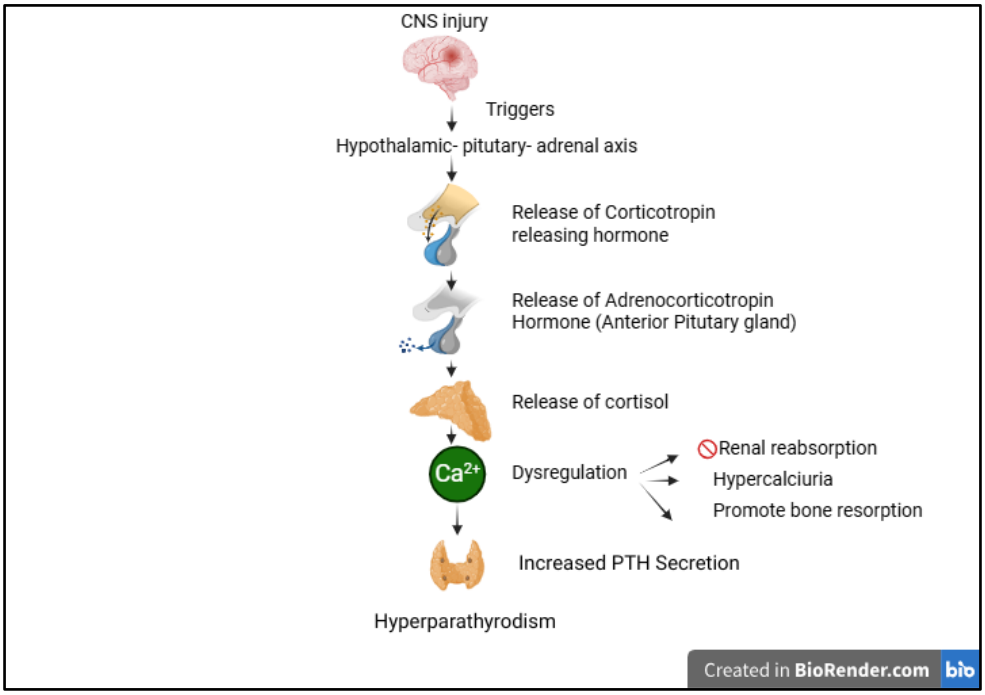

Figure: 3 Pathway from CNS Injury to Hyperparathyroidism via HPA Axis Activation

FUTURE PERSEPCTIVES

Recent research prompts a deeper examination of the possible hypothetical correlation between **Central Pontine Myelinolysis (CPM)** and **hyperparathyroidism**, particularly through the shared pathophysiology of **electrolyte imbalance and osmotic stress.** Although a direct clinical link between CPM and Hyperparathyrodism has not been robustly established yet, future studies exploring this association could open novel preventive strategies. Understanding, how persistent CNS injury influence the regulation of parathyroid gland and calcium levels and offer new insights into neuroprotective approaches and calcium regulation. Early diagnosis and tight control of sodium levels without rapid correction may emerge as crucial measures not just to prevent organ damage but also to mitigate unexpected endocrine complications like Hyperparathyrodism. Thus, future interdisciplinary research integrating **endocrinology and neurology** is vital to uncover these complex interactions.

CONCLUSION

Although Central Pontine Myelinolysis (CPM) remains relatively rare, its prevalence is notably higher among patients with chronic systemic illnesses such as liver disease, alcoholism, renal failure, and severe electrolyte disturbances. Recognizing potential comorbidities like hyperparathyroidism could significantly improve early detection and prevention strategies. Current treatments for CPM are largely supportive, with no established curative therapies, emphasizing the urgent need for preventive approaches based on metabolic and endocrine stabilization.

Understanding the stress-induced hormonal shifts that may contribute to CPM, such as cortisol-driven hyperparathyroidism and calcium-phosphate imbalance, could pave the way for novel therapeutic targets. Future research should focus on validating this proposed neuroendocrine-inflammatory pathway, exploring pharmacological interventions that stabilize both osmotic and hormonal imbalances, and developing clinical protocols for early risk assessment. A multidisciplinary management strategy, combining neurology, endocrinology, and critical care, holds promise for improving outcomes and reducing the long-term disability associated with CPM.

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