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IMMOBILISATION AND COGNITIVE DECLINE IN BRAIN INJURY - CALCIUM THE CONNECTING LINK

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Abstract : Immobilization hypercalcemia (IH) is a rare entity. It is seen in patients with long term immobilization, like spinal cord injury or long bone fracture, particularly in children and adolescents. Here we report a case of Immobilization hypercalcemia in a patient with Brain injury, which was clinically unnoticed and later presented with complications, which has significant impact on the cognition and affects neurological recovery. The exact pathophysiology of immobilisation related hypercalcemia is yet unknown, but rapid bone turnover is supposed to be involved in the process.We report a case of Immobilization hypercalcemia in a patient one year after traumatic brain injury. During the hospital stay, the patient had an episode of seizure. Routine blood investigations were normal except for high calcium levels. Further investigations revealed low parathyroid hormone, normal 1,25-dihydroxy vitamin D and high 24-hour urinary calcium. He was diagnosed to have IH after ruling out all other causes of hypercalcemia. Treatment is targeted to wards lowering the serum calcium level by early mobilisation and exercises, intravenous hydration with isotonic saline, frusemide, Calcitonin, Bisphosphonates which are conventional therapies. Newer treatment options include receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, denosumab. Physicians dealing with long term bed ridden patients should keep this as a differential diagnosis which helps in avoiding unnecessary investigations chasing the aetiology, annoying recurrences and preventing life threatening complications.

Keyword : Immobilisation, Hypercalcemia, Traumatic brain injury, Bisphosphonates

Introduction

Hypercalcemia is a common electrolyte imbalance which can induce multiorgan dysfunction with diverse systemic consequences such as renal symptoms (polyuria, polydipsia), intestinal symptoms (nausea, vomiting, and constipation), neurologic symptoms (weakness, cognitive decline) and cardiac symptoms (Short QT interval, hypertension). Hypercalcaemic crisis (Calcium > 16 mg/dl) endangers the patient with encephalopathy, renal failure and death. Commonly encountered cases of hypercalcemia are malignancy, primary hyperparathyroidism, and chronic granulomatous disease.(1) Immobilisation long ago an established cause of hypercalcemia, is rarely clinically suspected, detected and managed accordingly. Immobilisation hypercalcemia was first described in an adolescent with fracture in 1941 by Albright, but still this entity remains under appreciated.(2) IH may be seen after orthopaedic fractures, spinal cord injury, Guillain Barre Syndrome, patients with burn injuries and in astronauts after exposure to microgravity in space. (3)(4) This disorder is more common in patients in children, adolescent and geriatric population and in patients with quadriplegia than it is in persons with paraplegia. (5)(6) The mechanism of IH is yet unclear, it is believed that loading promotes bone formation and unloading promotes bone resorption through signalling of mechanosensor osteocytes. With immobilization, the loading response required for bone formation and suppression of bone resorption is significantly reduced, leaving resorption unopposed.(7) Immobilisation stimulates osteoclastic bone resorption which causes calcium loss from the bones and hypercalciuria. When calcium efflux from bone exceeds the capacity of the kidney to excrete calcium it results in hypercalcemia. For the diagnosis of immobilization-related hypercalcemia, all the other causes of PTH- and vitamin Ddependent hypercalcemia should be carefully excluded.(8) Immobilized patients with pre-existing states of high bone turnover (particularly, adolescents and patients with Paget's disease, thyrotoxicosis or primary hyperparathyroidism), and/or reduced renal function are at the risk of developing severe hypercalcemia.(5)(9). IH results in increased rates of bone resorption as confirmed by elevated calcium/creatinine ratios (>0.50)and urinary hydroxyproline/creatinine ratios (>0.033).(10) The primary mode of management of Immobilization hypercalcemia is inhibition of bone resorption by therapeutic agents like bisphosphonates and enhanced excretion of calcium by increased fluid intake and diuretics through renal tubules. A passive mobility or weight-bearing rehabilitative program is the curative treatment and should be instituted as early as possible. Control of the underlying illness generating immobilization and early initiation of passive mobility or weight bearing is crucial to faster recovery or alleviation of effects of immobilization.

Case Report:

40 year old male admitted for second phase of rehabilitation one year following traumatic brain injury. GCS at admission was E 4 M 4 Vt. RLA Stage (confused, inappropriate, and not agitated). (11) During his stay in the hospital he had an episode of generalized tonic clonic seizure, All the blood investigations were normal except serum calcium (ionized calcium -13.2). There was no previous history of seizure, patient was on antiepileptic's prophylactically (Levetiracetam) since 1 year. Hypercalcemia work up (Alkaline phosphatase 118, Vitamin D- 22, PTH< 1)

directed the diagnosis towards PTH independent Hypercalcemia. Thyroid and adrenal function tests were in normal limits. Abdominal ultra-sonographic examination did not show nephrolithiasis. Ruling out other causes (Malignancy work up, Hypervitaminosis D, Sarcoidosis) of hypercalcemia pointed towards the diagnosis of immobilization related hypercalcemia. Serum creatinine was raised during this period, suggesting which again reverts to normal after adequate hydration. 24 hour Urinary calcium was 489mg (Normal < 240 mg; male); 24 hour Urinary creatinine was 548 mg (1.0-2.0 G/ DAY). Immobilisation leads to increased bone resorption as judged by raised fasting urinary calcium to creatinine concentrations 890mg/g (normal12-35 mg/g). Bone scanindicated towards metabolic bone disease and urinary parameters indicated significant resorption. Mobilization and adequate hydration were initiated as initial measures of therapeutic treatment.100 ml/hour of normal saline to expand intracellular volume did not show any change in serum calcium levels. Risk of cognitive decline, attention and memory impairment (neuropsychiatric problem of hypercalcemia) in addition to seizure in this case, resulted in significant detoriation of cognitive function from RLA 5 to RLA Stage 3.(12) RLA Stage 5 (Confused, Inappropriate, Non agitated Response)- Patient gives random, fragmented, and non-purposeful responses to complex or unstructured stimuli – Simple commands are followed consistently, memory and selective attention are impaired, and new information is not retained) RLA 3 (Localized Response) - Patient responds specifically and inconsistently with delay to stimuli but may follow simple command for motor action.(13) Serum calcium levels first noticed were 13. 3mg% and the subsequent values were in the range of 11mg%. Serum calcium remained high after hydration and diuretics, antiresorptive agent, Zolendronic acid was given. (4 mg in 500 ml normal saline over 4 hours, single dose). One day after Zolendronic injection, the calcium levels dropped from 11.8 mg % to 10.7 mg% and on 3rd day was within normal limit, the lowest calcium level observed was 7.5 on the 4th day (one episode of hypocalcemia was observed).On 7th day it was 7.98mg% reverting back to normal. Repeat Calcium after 2 weeks was within normal range. In our case we have not evaluated the bone markers which would have probably aided the diagnosis. During first visit, 2014 February, one year earlier serum calcium levels were marginally on the higher side (10.9 mg %) Routine blood results showed raised alkaline phosphatase and supressed PTH levels. With clinical background of restricted right elbow ROM and high alkaline phosphatase levels heterotopic ossification (HO) was confirmed with roentogram findings. Treatment of elbow heterotopic ossification was initiated with bisphosphonates (Alendronate) and was continued for 6 months. Although the PTH levels were low and ALP was elevated, the repeat serum calcium levels (10.2 mg %) were just within normal limits and hence the case was not further evaluated. Bisphosphonates initiated for HO would have been helpful to correct the calcium leels during initial days. Prolonged immobilization after discharge, would have contributed to the high serum calcium levels. Stopping of bisphosphonates would have also added on to the rise of calcium causing the deleterious effect which would have contributed to seizures or cognitive decline. Hence for bed bound brain injury patients who are at higher risk of deleterious effects of immobilization, a detailed history of immobilization (minimum mobilisation hours/days and mode of mobilization) should be taken and investigation of serum electrolytes should include serum calcium levels along with serum sodium for cognitive decline. Serum calcium checked at least once every visit, may prevent complications which significantly detoriate the progress, such as cognitive decline in our case. Although seizures cannot be directly attributed to hypercalcemia, the same cannot be ruled out. Careful monitoring of metabolic derangements is essential in high risk group of patients.

Discussion

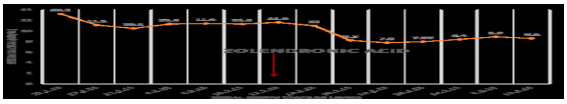
Immobilization hypercalcemiais an entity worth considering as differential diagnosis in patients with long term immobilisation. It usually develops 4-6 weeks of immobilisation (2 weeks – 6 months), but in our case it was after18 months of injury. (14) In this case, the patient was adequately hydrated with intravenous (IV) normal saline which enhances the glomerular filtration rate and the excretion of calcium in the urine. As in our case intravenous saline (with furosemide) did not show a significant response to control hypercalcemia, hence second line medications were preferred.(15) Adequate kidney function should be ensured to have appropriate response to IV saline as impaired renal function with reduced GFR will not reduce hypercalcemia. (16) Severe acute hypercalcemia is dealt with calcitonin, as it promptly and effectively decreases the serum calcium concentration but its effect is to a few days only because of development of tachyphylaxis.(17) If isotonic saline infusion do not decrease serum calcium concentrations we need to shift to other treatment choices such as bisphosphonates. (14) Bisphosphonate acts by inhibiting osteoclast-mediated resorption and by reducing osteoclast viability and it is approved for the treatment of hypercalcemia of malignancy. The drug is administered as a single intravenous (IV) dose and rapidly lowers serum calcium within 3 days. (18) Zolendronic acid is another bisphosphonate approved for the treatment of hypercalcemia of malignancy. In randomized clinical trials, zolendronic acid was more effective than pamidronate in lowering serum calcium levels, with a longer duration of action.(19) Alendronate, Ibandronate and Etidronate are other bisphosphonates that can be used for the treatment of IH which act by inhibiting bone resorption.(18) In patients with significant renal impairment, bisphosphonates may be a contradiction. Desosumab, a monoclonal antibody against receptor activator of nuclear factor-(RANK) ligand/ (RANKL) is currently used for hypercalcemia in patients with renal insufficiency.RANKL is present on osteoblasts, whereas RANK is present on osteoclasts. In bone physiology, osteoblasts activate osteoclasts through RANKL/RANK binding (20). Denosumab prevents binding of RANKL to RANK and thus inhibits bone resorption in a similar manner as physiological osteoprotegerin(21). Denosumab, unlike bisphosphonates is not contraindicated in patients with renal insufficiency, and has prolonged action than that of calcitonin, which makes it the treatment of choice in such cases (22)

Conclusion

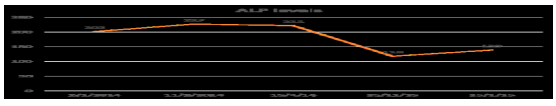
IH, a known entity, is highly underestimated, in clinical scenario. Physiatrists should be aware of this condition as hypercalcemia can cause significant neuromuscular impairment, along with other systemic complications, which can be deleterious in cognitive rehabilitation following traumatic brain injury. Early diagnosis and prompt correction of IH, can prevent unnecessary investigations, unwanted recurrences and potentially life-threatening complications.

Abbreviations:

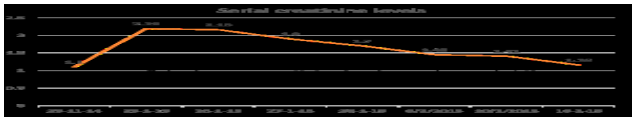
RLA Scale: Rancho Los Amigos Scale
GCS : Glasgow Coma Scale
GFR : Glomerular filtrartion rate
RANK: Receptor activator of nuclear factor



Graph showing serial monitoring (X axis-Dates) of serum calcium levels (Y axis). Significant drop in serum calcium levels is observed after giving Zolendronic acid.



Graph showing serum ALP levels, with significant drop observed after initiation of Risedronate and Indomethacin. (ALP; Alkaline phosphatase)



Graph showing serum creatinine levels, with the peak correlating with raised serum calcium levels. This may point towards impaired renal ability to compensate for hypercalciuria.

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