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Case Report

Severe hypocalcemia as a cause of transient ischemic attack? A debatable case and evidence from literature

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Abstract

Hypocalcemia and transient ischemic attack (TIA) are different medical disorders; however, limited evidence suggests a possible link between the two. The underlying pathomechanisms by which hypocalcemia may cause cerebrovascular damage are difficult to comprehend. The aim of the study was to present an individual experiencing TIA that possibly due to severe hypocalcemia that associated with hypoparathyroidism after total thyroidectomy; and to explore the available evidence of its cause-effect relationship through available literature. A 68-year-old man presented to Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia with complaints of weakness, especially in the right limbs that had worsened in the last week. The patient experienced unconsciousness for an hour before the admission; disorientation and anterograde amnesia over the time of recovering of consciousness. Other complaints included frequent muscle cramps, numbness in both arms and legs, dizziness, swallowing difficulty, nausea, and vomiting. The patient had a history of total thyroidectomy for a large struma diffuse 18 years ago and was prescribed several medications. However, the patient was overwhelmed by forgetfulness which had become more frequent in recent months resulting in medication nonadherence. The vital sign was stable and Chovsteck's sign was positive. The Montreal Cognitive Assessment (MoCA) revealed impairment in the visuospatial/executive component and delayed memory. Laboratory tests revealed severe hypocalcemia, altered thyroid function, hypomagnesemia, elevated D-dimer and fibrinogen, and vitamin D deficiency. TIA and severe hypocalcemia were proposed as the diagnosis. Prompt initiation of appropriate treatment, including calcium supplementation, anticoagulation, and neuroprotective agents, led to significant clinical improvement. Evidence from available literature suggests that there is a possible link between severe hypocalcemia and TIA that occurred in this patient. However, more studies are warrant to establish this cause-effect relationship.

Keywords: Ischemic event, hypoparathyroidism, total thyroidectomy, hypocalcemia, TIA

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Introduction

Transient ischemic attack (TIA), also known as a mini-stroke, is a transient episode of neurological dysfunction, often lasts for less than 24 hours, caused by a temporary blockage of

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blood flow to a certain part of the brain, spinal cord, or retinal ischemia without acute infarction or tissue injury [1]. TIA is different from stroke, as its ischemia is reversible; however, the risk of developing a stroke after a TIA is increased [1]. This corresponds to an increase in the key risk factors for ischemic events, such as hypertension, diabetes, obesity, smoking, dyslipidemia, atrial fibrillation, heart valve disease, and vasculitis [1]. Other risk factors and risks for severe ischemic stroke such as homocysteine, metabolic syndrome, insulin resistance, microalbuminuria, and altered serum calcium are increasingly being studied [2].

Electrolyte disturbances, such as calcium, are often found in stroke patients causing a possibility to affect clinical outcomes, which is triggered by neuronal changes at the cellular level caused by hypoxia [3]. Hypocalcemia due to hypoparathyroidism is the most frequent complication of thyroid and parathyroid surgeries [4]. The incidence of postoperative hypocalcemia is 1.2–40% and permanent hypoparathyroidism is approximately 3% of individuals with thyroid and parathyroid surgeries [5]. Permanent hypoparathyroidism could lead to the complication of chronic hypocalcemia which requires lifelong monitoring; affects morbidity and quality of life; and in severe cases could result in death [6]. In this case report, we present a patient with severe hypocalcemia due to complications of hypoparathyroidism after total thyroidectomy who experiencing TIA. Any evidence of cause-relationship between severe hypocalcemia and TIA is also explored through available literature.

Case

A 68-year-old man presented to Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia with complaints of weakness, especially in the right limbs that had worsened in the last week. The patient experienced unconsciousness for an hour before admission, the patient experienced disorientation and anterograde amnesia over the time of recovering from unconscious. Other complaints included frequent muscle cramps, numbness in both arms and legs, dizziness, difficulty swallowing, nausea, and vomiting. The patient had a history of total thyroidectomy for a large struma diffuse 18 years ago and has been prescribed levothyroxine 100 mcg once daily, calcium supplement 500 mg for each 8 hours and calcitriol 0.25 mcg twice a day. However, the patient was overwhelmed by forgetfulness which had become more frequent in recent months resulting in medication nonadherence. The patient had no history of high blood pressure, smoking, diabetes, or a family history of ischemic heart attack.

The physical examination results showed full alertness; blood pressure 145/98 mmHg; heart rate 88 beats/min; respiratory rate 20 breaths/min; temperature 36.2^{o}C; and a body mass index (BMI) of 18.9 kg/m^{2}. An asymmetrical facial droop was found, Chovsteck's sign was positive, and post-thyroidectomy cicatrix was present in the neck. The motor muscle strength examination for the right extremity revealed a score of four, consistent with right-sided hemiparesis, and the neurological examination revealed nerve IX paresis. The Montreal Cognitive Assessment (MoCA) revealed impairment in the visuospatial/executive component and delayed memory.

One day after admission, laboratory examination results indicted serum calcium 3.0 mg/dL, serum potassium 4.0 mmol/L, magnesium 1.5 mg/dL, albumin 3.6 g/dL, random blood glucose 146 mg/dL, D-dimer 3,560 ng/mL, fibrinogen 412 mg/dL, and vitamin D (25-OH-D) 17.22 ng/mL. Thyroid function tests were as follows: free thyroxine (FT4) 23.56 pmol/L and thyroid stimulating hormone (TSH) 1.58 μIU/mL. The electrocardiogram (ECG) showed ischemia at lateral leads (I and aVF) and prolonged QT. Echocardiography demonstrated a decreased left ventricular systolic function; hypokinetic at the anterior, anteroseptal, and inferoseptal wall; and grade 1 left ventricular diastolic dysfunction. The computed tomography (CT) scan of the head revealed senile cerebral atrophy. The patient was then diagnosed with TIA and severe hypocalcemia.

The patient was administered low molecular weight heparin (LMWH) enoxaparin sodium 0.6 ml/12 hours subcutaneously, intravenous (IV) piracetam 12 g/12 hours, IV mecobalamin 500 mg/12 hours, IV calcium gluconate 2 g in dextrose 5% 50 cc for one hour every 12 hours, calcium lactate tablet 1,000 mg twice a day, vitamin D tablets 1,000 UI twice a day, levothyroxine 50 ug once daily, atorvastatin 40 mg once daily, valproic acid syrup 15 ml twice a day, and folic acid 1,000 mcg once daily. Within 24 hours of the treatment, the patient showed clinical improvement

significantly. The muscle strength became normal with a full score of five in all limbs. Difficulty of swallowing, nausea, and vomiting was recovered. Calcium level increased to 8.9 mg/dL.

Discussion

TIA in severe hypocalcemia is unusual and may not be encountered frequently in clinical practice. The coexistence of severe hypocalcemia and TIA might pose diagnostic difficulties as they pose overlapping symptoms and the possibility of delayed or missed diagnosis. TIA is caused by one of several pathophysiologic cerebral blood flow processes: (a) lacunar or small vessel TIA, is related to intrinsic vascular factors, such as atherosclerosis, inflammation, aneurysms, or venous thrombosis, (b) embolic TIA, originates distantly from the brain such as embolus from the heart or extracranial deposit to intracranial circulation; and (c) low-flow TIA, causes insufficient cerebral blood flow such as decreased perfusion pressure, vascular spasm, or increased blood viscosity [7]. Low-flow TIA demonstrates the possible mechanism of TIA in the patient of this case report due to decreased cerebral blood flow.

This patient had multiple comorbidities that may contribute to the development of the cerebrovascular episode, including hypoparathyroidism related to total thyroidectomy, vitamin D deficiency, compliance issue, and mild cognitive impairment. All of those lead to worsening the condition of hypocalcemia. Hypocalcemia can arise in vitamin D deficiency, hypoparathyroidism, renal disorders, and many others.

Total thyroidectomy of the patient could be the starting point of the hypocalcemia condition. Several most frequent mechanisms involved in hypoparathyroidism post thyroid surgery are direct damage to the thyroid gland either due to injury to the vascularization system, mechanical damage, or intentional or accidental excision of part or all of the gland [8]. Low parathyroid hormone level leads to hypocalcemia and persistent hypocalcemia is defined as serum calcium below 2.0 mmol/L (8 mg/dL) and or requiring supplementation with calcium and/or calcitriol for more than six months after total thyroidectomy [6]. There are many symptoms of severe hypocalcemia such as seizures, carpopedal spasm, paresthesia, uncontrolled muscle movements, QT interval prolongation, heart failure, laryngospasm, and cardio-cerebrovascular complications [9,10]. Prolonged QT was present in the patient ECG suggesting severe hypocalcemia.

There are some risk factors that may increase the risk of hypocalcemia and hypomagnesemia after total thyroidectomy such as age over 40 years, female gender, hyperthyroidism, greater extent of surgery, post-surgery level of parathyroid hormone less than 8 pg/mL, post-surgery hypomagnesemia, diabetes, prolonged proton pump inhibitor intake, and teriparatide intake [11,12]. Some identified risk factors cannot be treated before, during, or after surgery; therefore, calcium carbonate, vitamins, and minerals are recommended for all patients undergoing thyroid surgery to prevent hypocalcemia symptoms [11,12]. The patient of the case report had several risks mentioned, of which are age, hyperthyroidism, and hypomagnesemia.

TSH suppression using levothyroxine is a routine therapy given to patients who have total thyroidectomy with or without radioactive iodine ablation. Subclinical or overt hyperthyroidism due to supraphysiological doses of levothyroxine for TSH suppression can be a risk factor for ischemic stroke and can also trigger angina or other cardio-cerebrovascular disease. Systolic hypertension, arterial stiffness, increased low-density lipoprotein (LDL) cholesterol oxidation, hypercoagulability, and arrhythmias are thought to be the most likely mechanisms [13].

Hypocalcemia has been linked with ischemia events, yet still sparks a debate about whether hypocalcemia and TIA are associated since current studies have not explored it comprehensively. However, several studies have reported ischemic events due to hypocalcemia [14-17] such as ischemia which leads to cardiogenic shock secondary to hypocalcemia [14], and coronary spasm due to hypocalcemia [15-17]. Only one report of ischemia event in the brain due to hypocalcemia [18]. Based on those available evidence, there is a possible link between severe hypocalcemia and TIA that occurred in patient.

The pathophysiological mechanisms underlying severe hypocalcemia and the development of TIA are not entirely clear. Some hypotheses, however, have been proposed. Serum-ionized calcium undoubtedly contributes to the etiology of ischemic stroke by altering the cycle of cytotoxic events leading to ischemic cell death [19]. Low blood flow in the brain below 10–15

mL/100gr/min will provoke ischemia [20]. If the blood flow to the brain is reduced to 6–8 mL/100gr/min, there will be a disturbance in the adenosine triphosphate (ATP) pump causing an increase in extracellular potassium, intracellular calcium, and cellular acidosis leading to histologic cell necrosis [21]. The accumulation of intracellular calcium may cause neuronal damage by initiating cytotoxic processes that lead to cell death [18,22]. Elucidating the exact pathophysiological mechanism that may underlie TIA in hypocalcemia is challenging, especially since it is unclear whether serum calcium level exert a primary effect on TIA or reflect a secondary epiphenomenon of ischemic stroke severity. Further studies are therefore needed to elucidate the relationship between hypocalcemia and TIA.

Conclusion

Permanent hypoparathyroidism is prone to chronic hypocalcemia, which necessitates lifetime treatment. Although the exact pathophysiological mechanism of how severe hypocalcemia could cause TIA is not well understood, evidence suggests the possibility of the relationship between hypocalcemia and TIA. Therefore, it is critical to regularly monitor the calcium levels in patients with a thyroid or parathyroid surgery to avoid TIA and other hypocalcemia-associated complications. Calcium supplementation is the most effective strategy to date.

Ethics approval

The patient provided written informed consent to be published as a case report.

Competing interests

The authors declare that there is no conflict of interest.

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Underlying data

All data underlying the results is available as part of the article and no additional source data are required.

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