International Journal of Medical and Pharmaceutical Case Reports

9(3): 1-5, 2017; Article no.IJMPCR.33721
ISSN: 2394-109X, NLM ID: 101648033

Hypoparathyroidism, Brain Calcifications and Seizures

Aldo Bertoli[1*], Alessia Valentini[1], Alessandro Mauriello[2] and Umberto Tarantino[3]

[1]Department of System's Medicine, University of Rome "Tor Vergata", Viale Oxford, 8100133 Rome, Italy.
[2]Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Viale Oxford, 8100133 Rome, Italy.
[3]Department of Orthopeadics and Traumatology, University of Rome "Tor Vergata", Viale Oxford, 8100133 Rome, Italy.

Authors' contributions

This work was carried out in collaboration between all authors. Authors AB and AV wrote the first draft of the paper and managed the literature searches. Author AM performed the histologic examination. Author UT performed hip replacement surgery and bone biopsy. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJMPCR/2017/33721
Editor(s):
(1) Nurhan Cucer, Medical Biology Departmnt, Faculty of Medicine, Erciyes University, Turkey.
Reviewers:
(1) Andrew Dale, OBGYN University of New Mexico Hospital, USA.
(2) Gehad A. El-Nakib, Mansoura University Hospitals, Egypt.
(3) Najib Murr, Southern Illinois University School of Medicine, USA.
(4) Güner Çelik, Beyhekim State Hospital, Konya, Turkey.
(5) Diana Dmitrenko, V.F. Voino-Yasenetsky Krasnoyarsk State Medical University, Russia.
Complete Peer review History: http://www.sciencedomain.org/review-history/19444

Case Study

Received 26th April 2017
Accepted 5th June 2017
Published 9th June 2017

ABSTRACT

Background: The most common cause of hypoparathyroidism is iatrogenic in the context of surgical procedures to the neck and commonly the thyroid gland. Hypoparathyroidism is characterized by hypocalcaemia, hyperphosphatemia and low or inappropriately normal levels of parathyroid hormone (PTH) and may be associated with multiorgan complications and variable clinical presentation. Seizures may be the only presenting symptom and may result in antiepileptic therapy. Knowledge of all possible consequences of hypoparathyroidism is essential for correct patient management.

**Corresponding author: E-mail: aldo.bertoli@uniroma2.it;*

Case Description: A 76-year-old woman was admitted due to loss of consciousness, seizures and hypocalcemia. She had had total thyroidectomy over 60 years ago for toxic goiter, complicated by permanent hypoparathyroidism. Her calcium levels were erratic, treated with calcium, colecalciferol and calcitriol. She developed progressive confusion, and had convulsive episode before hospitalization. Clinical investigation revealed widespread cerebral calcifications, EEG abnormalities and diffuse skeletal abnormalities. Later, during hip replacement surgery, bone histopathology showed bone marrow substitution by fibrous tissue undergoing ossification. All clinical problems occurring to the patient can be referred to hypoparathyroidism and consequent hypocalcemia not adequately corrected, including early bilateral cataracts.

In the absence of consolidated hormone replacement therapy, treatment of hypoparathyroidism is represented by vitamin D and calcium supplementation. In our case, the total absence of PTH and its role on vitamin D activation did not allow optimal control of serum calcium, despite normal levels of 25-hydroxyvitamin D being observed. The achievement of target values in serum calcium was obtained only with calcitriol. Treatment with levetiracetam was thus suspended and no more seizures occurred at two year follow-up.

Conclusion: Awareness that convulsions can only be caused by hypocalcemia, even in the presence of organic brain injuries, can help patients avoid using unnecessary medications and their potentially harmful side effects.

Keywords: Hypoparathyroidism; hypocalcemia; seizures; brain calcifications; aging.

1. PRESENTATION OF CASE

In April 2013, a 76-year-old woman presented to the Emergency Department with generalized tonic clonic seizures. An intravenous infusion of diazepam (10 mg) was administered in the ambulance. According to her relatives, she had appeared confused over the last month and had sustained a convulsive episode three days before hospitalization. She was treated at home with furosemide, bisoprolol, levothyroxine and carbonated calcium alternated with cholecalciferol or calcitriol, which the patient took irregularly. Her past medical history included thyroidectomy at 14 years of age for toxic goiter, surgery for crystalline cataract at 52 years, a right mastectomy for cancer at 62 years and left hip arthroplasty at 70 years. On physical examination in the emergency room, the patient exhibited aphasia and dysarthria, with muscular contraction of the lower and upper limbs. Tests showed hypocalcaemia <1.25 mmol/L (2.12-2.55), with ionized calcium equal to 0.49 mmol/L (1.17-1.3). Electroencephalography (EEG) revealed paroxysmal slowing and spike-wave complexes in the front-temporal bilateral regions, with a clear left prevalence. A brain computerized tomography (CT) scan did not show acute lesions but confirmed the presence of diffuse calcifications of the basal ganglia in the cerebellum and at the level of periventricular white matter (Fig. 1A). The patient was treated intravenously with calcium gluconate infusion, leading to a complete clinical resolution of her condition. Levetiracetam was added as prescribed by a neurologist.

Upon admission to our department, she appeared lucid and oriented. Her mini-mental state examination score (MMSE), adjusted for age and education, was 30. The patient had no signs of latent tetany, but complained of stiffness in the dorsolumbar column and pain in the bones and joints of the hip which had not been operated on, resulting in decreased function. Tests performed during her hospital stay showed calcaemia 1.57 mmol/L (2.12-2.55), phosphatemia 1.68 mmol/L (0.87-1.45), parathyroid hormone (PTH) <0.27 pmol/L (1.47-7.56), vitamin D3 147 nmol/L (>74.88), thyroid stimulating hormone (TSH) 0.81 microUI/L (0.35-4.5), free triiodothyronine (FT3) 3.69 pmol/L (3.54-6.47) and free thyroxine (FT4) 19.87 pmol/L (10.30-22.52). Electrocardiography (ECG) showed a prolonged QTc interval consistent with hypocalcemia. Skeletal radiography found the presence of a diffuse thickening of the skull and the periosteum of the diaphysis of the long bones (Fig. 1A, 1C), the presence of syndesmophytes particularly evident in the lower back (Fig. 1B) and signs of osteoarthritis of the right hip. A dual-energy x-ray absorptiometry (DEXA) scan showed T-score values of +7.3 SD at the lumbar spine and +6.1 SD at the neck of the femur. The patient was treated with calcium and calcitriol, reaching stable levels of calcaemia (2.0-2.15 mmol/L). An orthopedic evaluation indicated prosthetic replacement of the right hip, which was carried out in a subsequent hospitalization. Histological examination of the proximal epiphysis of the femur showed a marked hypocellularity of the bone marrow that appeared replaced by fibrous tissue with areas of

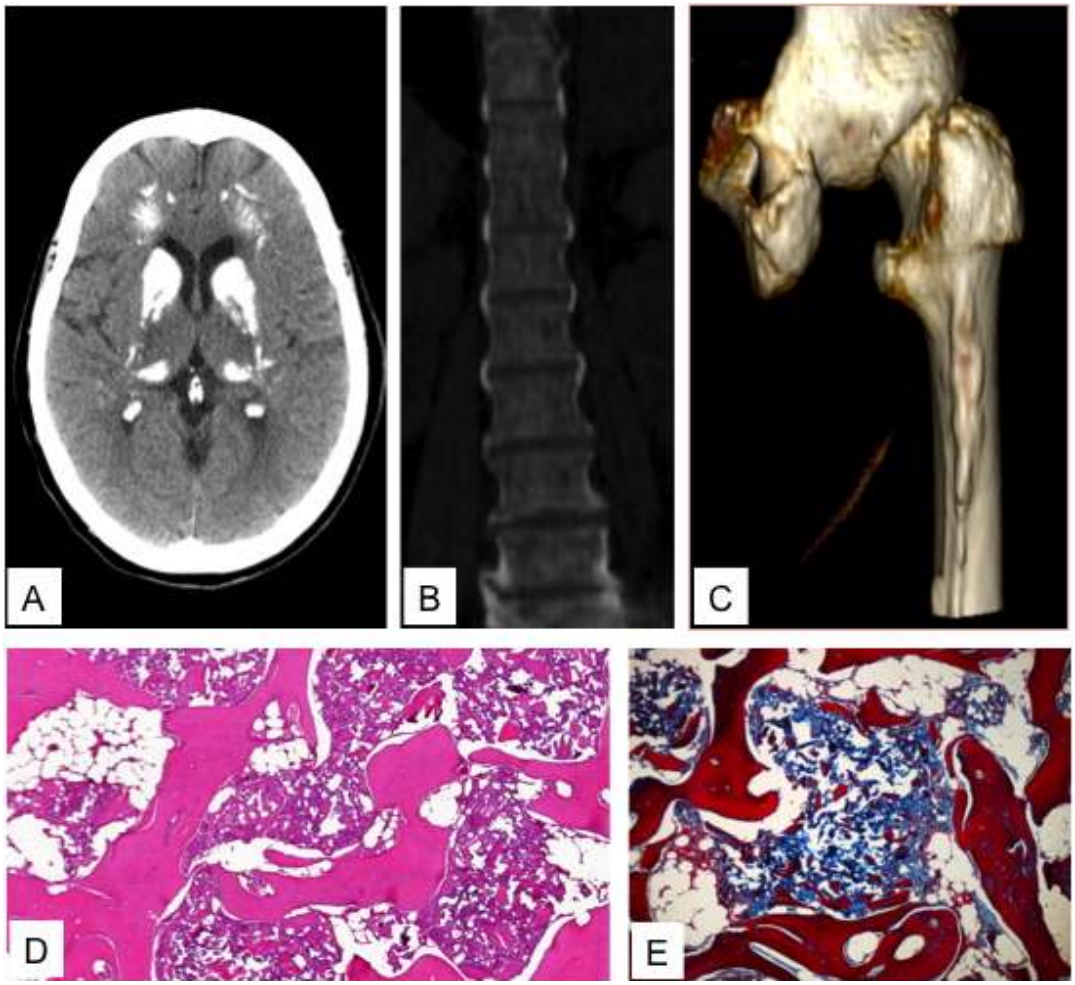

Fig. 1. Panel A: Brain CT showing the diffuse thickening of the skull and calcifications of periventricular white matter. Panel B: syndesmophytes in the lower back. Panel C: 3D CT reconstruction showing the diffuse thickening of the periosteum of the diaphysis of the femur. Panel D: At the level of the epiphyseal portion of femur closest to the shaft, bone marrow is replaced by fibrous tissue that undergoes ossification. Haematoxylin-eosin stain, 4x. Panel E: Masson trichromic stain, 4x; collagen is stained in navy blue, whereas bone in red

ossification (Fig. 1D, 1E). After being discharged, the patient had regular blood tests, with calcium levels stable at around 2 mmol/L. Treatment with levetiracetam was thus suspended and no more seizures occurred at two-year follow-up.

2. DISCUSSION AND CONCLUSION

Our patient developed all the possible consequences of hypoparathyroidism. The case of an elderly patient with long-lasting hypoparathyroidism and severe acute hypocalcaemia, complicated by widespread brain calcifications and bone alterations, and presenting with tonic-clonic seizures, raises the question whether the seizures can be attributed to the presence of cerebral calcifications or to hypocalcaemia alone.

Our diagnosis centered on the effects of a thyroidectomy performed more than 60 years ago, involving the bone and nervous systems, and focused on the critical importance of careful monitoring of calcium levels.

The prevalence of epilepsy rises progressively with increasingly aging populations worldwide [1]. In the elderly, clinical manifestations of epilepsy may differ: vague presenting complaints such as

confusion, altered mental status, or memory problems are common with new onset epilepsy [1].

Epilepsy may be associated with the presence of cerebral calcifications. Basal ganglia calcifications are also observed in Alzheimer's, Parkinson's, vascular dementia, and Lewy body disease [2]. Brain calcifications (Bilateral Striatopallidodentate Calcinosis, BSPDC) are also observed in hypocalcaemic syndromes, such as hypoparathyroidism, pseudo-hypoparathyroidism, and in some neurodegenerative syndromes, previously referred to as “Fahr’s disease” [2].

Acquired hypoparathyroidism is most commonly the result of inadvertent removal or irreversible damage to the glands during thyroidectomy. The absence of PTH prevents the mobilization of calcium from the bone, renal reabsorption of calcium and activation of the enzyme 1-alpha-hydroxylase renal. Hypoparathyroidism is characterized by hypocalcaemia, hyperphosphatemia and normal or inappropriately low levels of parathyroid hormone. Patients with hypoparathyroidism most often present with paresthesia, cramps, and tetany due to hypocalcaemia. Generalized tonic–clonic seizures can occur in hypocalcaemia and, significantly, may be the sole presenting symptom [3]. Long-standing hypocalcaemia, even without neuromuscular symptoms, is associated with the development of neuropsychiatric symptoms, calcification of the basal ganglia and extrapyramidal systems, premature sub-capsular cataract formation and seizures [4]. It is also associated with an increase in bone mineral density (BMD) due to a rise in bone mineralization secondary to suppressed bone turnover, as supported by lower levels of serum bone-specific alkaline phosphatase in patients with hypoparathyroidism.

In our patient, the complete absence of PTH resulted in an increase in bone mineral density, a thickening of the periosteum of the long bones and the progression of osteophytosis. She complained of stiffness in the dorsolumbar column and radiography showed spondyloarthropathy mimicking ankylosing spondylitis. The presence of spondyloarthropathy, cataracts and calcification of the basal ganglia is characteristic of long-lasting hypoparathyroidism. Besides the classic effect of 1,25-dihydroxyvitamin D on calcium regulation, it appears to reduce profibrotic signaling pathway and gene expression, leading to a decrease in collagen deposition [5]. An activation of the profibrotic pathway, secondary to 1,25-dihydroxyvitamin D deficiency, is consistent with the bone marrow fibrosis, calcification and hypocellularity observed in our patient.

Accustomed to chronically low levels of calcaemia, total thyroidectomy patients may remain asymptomatic for long periods of time. In the case of our patient, more than 60 years after surgery, severe hypocalcaemia resulting from non-adherence to the prescribed therapy was responsible for confusion, seizures and loss of consciousness that led to hospitalization. Irregular monitoring and control of calcaemia and phosphoremia enabled the formation of calcium deposits in the central nervous system, in particular in the basal ganglia, where several osteogenic molecules are expressed [6]. Chronic deficiency in active vitamin D, along with the absence of PTH, contributed to subperiosteal thickening and bone marrow fibrosis. Careful treatment with the active form of Vitamin D is imperative for the maintenance of low-normal calcaemia and normal calcium-phosphorus product, and for reducing complication risks. We concur with El Otmani et al. [4] who suggest that in patients with hypoparathyroidism and pseudohypoparathyroidism, epilepsy and psychiatric disorders are induced by hypocalcaemia and are reversible after being corrected.

Our patient developed seizures only at 76 years (more than 60 yrs after a total thyroidectomy was performed), when cerebral calcifications were documented, suggesting the possibility that calcifications and seizures were related.

A two-year follow-up of our patient further supports the hypothesis that hypocalcaemia alone is responsible for seizures observed in hypoparathyroid patients.

To conclude, this case study described the late consequences of chronic hypoparathyroidism, arguing that seizures and cognitive impairment may be the only clinical manifestations of hypocalcemia in hypoparathyroidism. We highlight the fact that the treatment used today for hypoparathyroidism, which is based on calcium and vitamin D, does not always allow for the effective control of calcaemia.

We also argue that recombinant PTH recently introduced in clinical practice in some countries, does not appear to have the characteristics of a true replacement therapy since lifetime treatment has not yet proven safe for the risk of bone cancer, and calcium and vitamin D supplements continue to be lifetime necessary.

Awareness that convulsions can only be caused by hypocalcemia, even in the presence of organic brain injuries, can help patients avoidi using unnecessary medications and their potentially harmful side effects.

Given that the consequences of hypocalcemia/ hypercalcaemia are often systemic but remain underestimated, this case is relevant to specialists in endocrinology, but also to general practitioners, internists, neurologists and geriatricians.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this paper and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Brodie MJ, Elder AT, Kwan P. Epilepsy in later life. Lancet Neurol. 2009;8:1019-1030.
2. Ramonet D, de Yebra L, Fredriksson K, Bernal F, Ribalta T, Mahy N. Similar calcification process in acute and chronic brain pathologies. J Neurosci Res. 2006; 83:147-156
3. Castilla-Guerra L, del Carmen Fernandez-Moreno M, Lopez-Chozas JM, Fernandez-Bolanos R. Electrolytes disturbances and seizures. Epilepsia. 2006;47:1990-1998.
4. El Otmani H, Lahlou I, Raji L, Omari S, Belmansour J, Moutaouakil F, Boulaajaj FZ, Mouden M, Gam I, Hakim K, El Moutawakil B, Rafai MA, Fadel H, Slassi I. Striatopallidodentate calcinosis, hypoparathyroidism and neurological features: A case series study. Rev Neurol (Paris). 2013;169:495-501.
5. Artaza JN, Norris KC. Vitamin D reduces the expression of collagen and key profibrotic factors by inducing an antifibrotic phenotype in mesenchymal multipotent cells. J Endocrinol. 2009; 200:207-221
6. Goswami R, Millo T, Mishra S, Das M, Kapoor M, Tomar N, Saha S, Roy TS, Sreenivas V. Expression of osteogenic molecules in the caudate nucleus and gray matter and their potential relevance for basal ganglia calcification in hypoparathyroidism. J Clin Endocrinol Metab. 2014;99:1741-1748.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/19444