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Case Report

Familial primary hypoparathyroidism revealed by epileptic seizures in an adult patient

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Abstract

Epileptic seizures can reveal familial primary hypoparathyroidism in adult patients. Computed-tomography evaluation is sufficient for diagnosis of secondary intracranial calcifications. Genetic tests and genetic advice are necessary in familial primary hypoparathyroidism.

Keywords: Epileptic seizures, Primary hypoparathyroidism, Genetic advice, neuroimagistic investigations

Abbreviations

PTH - Parathyroid hormone; **GCM_2** -extracellular calcium-sensing receptor G -protein coupled; **PH** - primary hypoparathyroidism, **IQ**- intelligence quotient; **CT**-computed tomography, **MRI**-magnetic resonance imaging, **EEG**-electroencephalographic examination, **EKG**- electrocardiogram, rhPTH-recombinant human parathyroid hormone.

INTRODUCTION

Familial primary hypoparathyroidism is a rare condition, a heterogenous mix of disorders, determining a state of inadequate parathyroid hormone activity.

Autoimmune causes include type 1 autoimmune polyglandular syndrome (HAM syndrome), due to destruction of parathyroids glands and also sporadic or familial forms. The average period for development of hypocalcemia in these form is 7 years (with a range from 6 month to 20 years) (Brandi et al., 2016).

Congenital causes include isolated primary hypoparathyroidism, X-linked PH (band Xq26-Xq27), autosomal-recesive PH, DiGeorge syndrome, chromosomal defects dup(1q), del(5p), dup(8q), del(10q), del(22q), monogenic PH, microdeletions 22q11 or isolated autosomal dominant/recessive conditions, Zellweger syndrome, Kearns Sayre syndrome, Barakat syndrome, fetal alcohol syndrome (Gonzales-Campoy, 2018).

Activating mutations of the extracellular calcium-sensing receptor G -protein coupled GCM_2 lead to hypocalcemia in the family forms of primary hypoparathyroidism. The intracellular mecanisms whereby activation of this receptor lead to inhibition of PTH exocitosis is unknown (Gonzales-Campoy, 2018).

CASE REPORT

A 36 year old male patient was admitted in our clinic for a tonico-clonic epileptic seizure that occured at home and repeated itself in hospital. From childhood, the patient had 1-2 seizures per year.

A border-line intellectis was associated with a moderate cranial dysmorphism. Due to a low frequency of seizures, the patient had never been neurologically

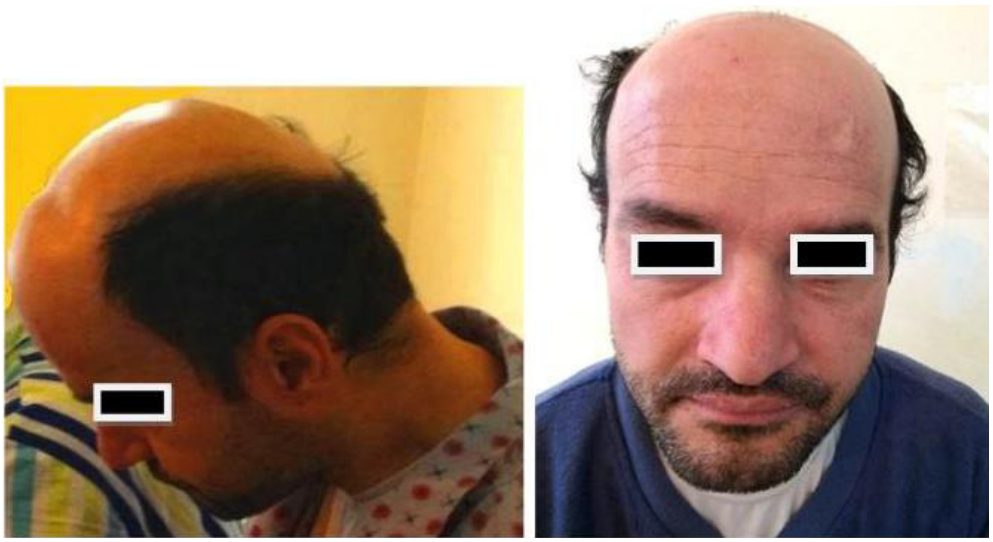

Figure 1. Cranial dysmorphism

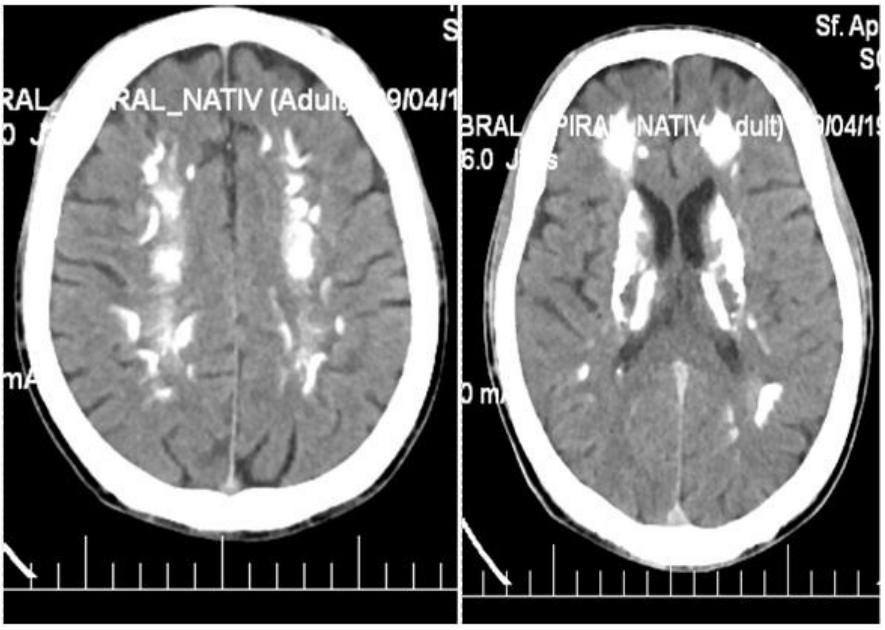

Figure 2. Brain CT- multiple bilateral intracerebral, macro- and micronodular calcification.

examined before, but he was diagnosed with hypocalcemic tetany and, during chilhood, he was treated with calcium supplements. Border-line intellect allowed schooling until secondary education.

The patient has no other personal pathologyc history, but he has a 4 year old son diagnosed with epileptic seizures and hypocalcemia, with sever mental retardation, troubles in community integration, psychomotor agitation episodes, who could not be trained.

The patient has a slight cranial dysmorphism, with a turicephalic aspect and prominence of the frontal bones, has an IQ of 84, presents bradylalia, bradypsychia and does not show any signs of neurological outbreak.The clinical signs of hypocalcemia are absent- figure 1.

Neuro-imagistic evaluation performed by brain-CT and MRI show multiple intracerebral, macro- and micronodular calcifications located in basal ganglia, periventricular and subcortical white matter - bilaterally, as well as in the cerebellar hemispheres – figure 2.

Biochemically, the following data was obtained: total serum calcium - 5.7 mg/dl, ionic calcium - 2.61 mg/dl,

phosphorus level-6.48 ml/dl, parathormone -3 µg/ml, normal magnesium levels, 1,25-dihydroxyvitamin D_3-12 ng/ml. There were no other changes in the blood biological constants.

EEG revealed a basic hypovolted pathway without intercritical pathological traits.

EKG showed a net increase amplitude of T waves, in the absence of changes in the blood ionogram (normal potassium level).

The echography of the parathyroid and thyroid glands showed a normal aspect. No other organ lesions were determined (without renal lithiasis). The diagnosis of multi-glandular disease (HAM syndrome) was not supported.

Clinical and paraclinical data have shown the suspicion of familial primary hypoparathyroidism with genetic determinism. Hypoparathyroidism was confirmed by hypocalcemia, hyperphosphorymia and decreased parathormone levels.

For microdeletions 22q11.2/DiGeorge syndrome, the FISH test was performed with locus-specific DNA probes for TUPLE1 (HIRA), TBX1, SLC25A1 (CTP), CLTD and SHANK3, ARSA, without identifying structural abnormalities to support the diagnosis. Subsequently, the molecular karyotype did not detect any change with clinical pathogenic arr(1-22)x2, (X,Y)x1 significance, but the method does not detect balanced structural chromosomal anomalies, mosaicism in small percentages, small mutations, polyploidy, uniparental disomy, and chromosomal abnormalities below the detection limit of 60 kba can not be identified. No additional evaluations for GCM2 mutations were available.

A diagnosis of familial primary hypoparathyroidism, probably a sporadic familial form or with an unidentified genetic mutation has been established.

Anticonvulsant treatment with carbamazepine, calcium supplements and alfaD_3 has been administreated and rhPTH treatment was not available. The seizures have not reocurred. Calcilytics were not required.

The patient remains in clinical and paraclinically observation.

DISCUSSIONS

Primary hypoparathyroidism leading to hypocalcemia, revealed by epileptic seizures in adulthood is quite infrequent and it is a cause of treatable reccurent seizures.

Neurological manifestation range from minor signs of latent tetany to epileptic seizures due to hycalcemia or, more rarely, to intracerebral calcifications (Correia et al., 2012).

Prolonged hypoparathyroidism causes intracerebral calcifications - predominantly in basal ganglia, dentate nuclei and subcortical (Kiroğlu et al., 2010; You et al., 2008) and secondary epilepsy with recurrent seizures, refractory to treatment. Also, hypocalcaemia secondary to hypoparathyroidism may lead to seizure onset. Patients may experience epileptic seizures even in the absence of clinical signs of hypocalcemia (Acharya et al., 2012).

Differentiation between the two mechanisms that cause the epileptic seizures involves laboratory investigations (dosing of calcium, phosphorus, PTH) and neuroimaging (brain CT or MRI). However, there are situations that associate severe hypocalcaemia with macronodular intracerebral calcifications, in which case, the mechanism of epileptic seizures is difficult to determine.

CONCLUSIONS

In an adult patient with a significant heredo-collateral history (a son with the same symptomatology to be investigated), the association of hypoparathyroidism - recurrent (childhood) epileptic seizures - cranial dysmforphism, borderline intelect and the presence of intracerebral calcifications may suggest a diagnosis of primary hypoparathyroidism with genetic determinism.

In our case, the diagnosis was confirmed late in an adult patient who had not been investigated neurologically until the actual hospitalization, starting from the evaluation of tonic-clonic epileptic seizures. Macro- and micro- intracerebral calcifications have been correlated with changes in calcemia, phosphatemia and PTH levels.

Epileptic seizures can be explained by both hypocalcemia and intracerebral calcifications.

Genetic advice should be considered, with the patient already having a son with the same symptomatology.

The patient requires dispensarization, having a risk of developing kidney lithiasis.

The case shows the importance of hypoparathyroidism and secondary intracerebral calcifications as a cause of recurrent epileptic seizures.

Genetic testing and/or family screening are necessary in a patient with hypoparathyroidism of unknown etiology.

Informed Consent

The patient's informal approval has been obtained and recorded in the chart.

Author contributions

All the authors have equal contributions in this presentation.

Ethical approval

This article does not contain any studies with human participants performed by any of the autors.

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