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CONGENITAL PSEUDOHYPOPARATHYROIDISM – A LATE DIAGNOSIS

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Abstract

The purpose of this paper is to present a case of congenital pseudohypoparathyroidism, late diagnosed in a 22-year-old patient.

The patient's history revealed hypocalcaemia, diagnosed at birth and persistent despite the treatment with calcium. At 8 years old, the patient is diagnosed with epilepsy and receives treatment with Levetiracetam and Oxcarbazepine; at 12 years old she is diagnosed with dilatative cardiomyopathy and receives treatment with Spironolactone and Glycosides. At 22 years old, she visits our Internal Medicine Department with the suspicion of polymyositis and psoriasis. Clinical examination shows armonic short stature, fourth finger hypoplasia, laboratory findings show severe hypocalcaemia, the hand X-ray - third and fourth metacarpal hypoplasia, immunological tests were negative. All data leads to the diagnosis of congenital disease, and given the history of the patient and the evolution of the clinical manifestations we presume hypoparathyroidism or pseudohypoparathyroidism, therefore PTH is dosed – with normal values, and the diagnosis of congenital pseudohypoparathyroidism is established. The patient was referred to endocrinology, where genetic tests were performed to confirm the diagnosis.

In conclusion, in the absence of multiple pathology integration into a single disease, the diagnosis of the genetic disease is delayed. Therefore, it is important to have a comprehensive approach and collaboration between different specialties to establish the correct diagnosis.

Keywords: *congenital pseudohypoparathyroidism, hypocalcaemia, epilepsy, dilatative cardiomyopathy, GNAS1.*

Rezumat

Scopul lucrării este prezentarea unui caz de pseudohipoparatiroidie congenitală, care a fost diagnosticat tardiv, la o pacientă în vârstă de 22 de ani.

Istoricul pacientei a evidențiat hipocalcemie diagnosticată la momentul nașterii și care a

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persistat pe toata durata vieții, în ciuda terapiei cu suplimente de calciu. Ulterior pacienta dezvoltă la vârsta de 8 ani epilepsie, pentru care primește tratament cu Levetiracetam și Oxcarbazepină. La 12 ani este diagnosticată cu cardiomiopatie dilatativă și insuficiență cardiacă, pentru care primește tratament cu spironolactonă și glicozid digitalic.

Se prezintă în clinica medicală cu suspiciunea de polimiozită și psoriazis. Clinic, prezintă nanism armonic, hipoplazia degetului IV, iar investigațiile de laborator au arătat hipocalcemie severă, radiografia de mâini - hipoplazia articulațiilor metacarpofalangiene IV, CT cerebral - multiple calcificări cerebrale, teste imunologice negative. Toate datele duc la diagnosticul de boală congenitală, dat fiind istoricul pacientei și succesiunea evolutivă a manifestărilor, se suspicionează hipoparatiroidie sau pseudohipoparatiroidie, motiv pentru care se dozează PTH, cu valori normale, diagnosticându-se astfel pseudohipoparatiroidia congenitală. Pacienta a fost îndrumată spre endocrinologie, unde s-au efectuat teste genetice pentru confirmarea diagnosticului.

În concluzie, prin absența integrării tutoror patologiilor în cadrul unei singure boli, se întârzie diagnosticarea bolii genetice. De aceea, este importantă abordarea exhaustivă și colaborarea între diversele specialități pentru a stabili diagnosticul corect.

Cuvinte cheie: *pseudohipoparatiroidie congenitala, hipocalcemie, epilepsie, cardmiomiopatie dilatativa, GNAS1*

We are presenting the case of a 22 year old female patient, with insignificant medical history, who discloses the following history on anamnesis: at birth she presented hypocalcaemia, during the neonatal care she received calcium gluconate, with a rise in calcium levels and long term treatment recommendation of calcium at home, with no further investigation of neonatal hypoglycaemia. The patient was no longer monitored, until, at the age of 8, she developed generalised epileptic seizures, EEG documented. She receives antiepileptic treatment with Levetiracetam 350 mg and Oxcarbazepine 450 mg, under which the seizures attenuate and then disappear. Still, the patient's calcium levels during the admission remain low, which is why long-term treatment with calcium is recommended, with no further investigation of the cause of persistent hypocalcaemia. At the age of 12, the patient develops signs of heart failure clinically manifested through effort dyspnoea and she is admitted to Fundeni Clinical Institute, where she is diagnosed with DCM and receives heart

failure treatment – Digoxin 12,5 mg/day, Spironolactone 25 mg/day and Carvedilol 3,125 mg x2/day. The patient's calcium levels are low at admission this time as well, which is why she receives calcium treatment during admission which is further recommended to be administered at home, with no further investigation of the cause of the hypoglycaemia.

At present, at 22 years old, the patient is transferred to our clinic from the „Prof. Dr. Matei Balș" National Institute of Infectious Diseases for further investigations and suspicion of collagenosis. Approximately one month ago she presented right calf cellulitis, for which she received antibiotic treatment from Argeș County Hospital with ciprofloxacin, Augumentin and Vancomycin, becoming allergic to the latter, and the treatment was unsuccessful because the fever persisted, which is why she was transferred to „Prof. Dr. Matei Balș" INBI. Here, she continues to have fever, despite intensive antibiotic treatment (with meropenem, Tigecilcine, and Linezolid), the blood culture is negative, and because of tissue disorders getting worse, the patient is being administered corticotherapy, with partial benefit. On clinical examination, the patient presents a satisfactory general condition, growth retardation, skin with erythematous lesions evolved into placards, with intense epidermal peeling, poor dentition, retracted tendinitis in palms of hands, elbows and knees, resorption of second distal phalanx, MCF III and IV bilateral joint hypoplasia (Figure 1), holosystolic murmur of mitral regurgitation. A dermatologic consultation is solicited, as a result of which exfoliative dermatitis lesions are identified, with tinea amiantacee lesions on the scalp and a skin biopsy is recommended, which lays down the subacute spongiotic dermatitis diagnosis (eczema type), for which she receives topical treatment with hydrocortisone acetate ointment with vitamin A, betamethasone and salicylic acid cream, as well as betamethasone and gentamycin cream, with the improvement of the aspect of the skin lesions (Figure 2).

Paraclinically, the patient presents normochromic, normocytic anaemia, (haemoglobin = 9.3 g/dl), very high NT pro BNP (3854 pg/ml), very low levels of serum and ionized calcium (3.74 mg/dl, and 1.77 mg/dl), high levels of muscular cytolysis enzymes (CK = 449 UI/L and LDH = 622 UI/L), moderately low levels of C3 complement fraction (0.75 g/l).For autoimmune diseases screening autoantibodies are collected (FR, FAN/ANA, Ac anti-ADN double-stranded, Ac anti-Jo) which are negative, and the rest of the paraclinical investigations remain within normal ranges. A hand radiography is carried out, which does not present marginal erosions, but shows a hypoplastic aspect of metacarpal bones III and IV bilateral (Figure 3). Thoracic X-ray shows high diameters of the heart (Figure 4). Echocardiography shows a 28 mm left atrium, with a 12 cm^2surface, left ventricle in diastole with a 51 mm diameter and 38 mm in systole, normal levels usually, but when indexed to the total body surface of the patient (nanism), these levels are high. Mitral valves are distally thickened, especially the anterior mitral valve, with a 31 mm length of mitral ring. A mitral regurgitation grade 3 with eccentric jet, and ejection fraction of 30% is also observed. After the administration of intravenous calcium during the admission, the patient was re-examined on echography and an improvement of FEVS and exercise tolerance was noted, with a rise up to 45% (Figure 5). An ophthalmologic consultation is also performed, showing cortical and subcapsular

cataract LE>RE, with a recommendation for a surgical intervention for LE cataract, as well as cerebral MRI, which presents native aspect within normal ranges (Figure 6).

Following the investigations performed that show a sever hypocalcaemia (3,74 mg/dl) and the clinical context of short stature, dilatative cardiomyopathy, seizures, MCF IV joint hypoplasia, poor dentition and mental deficit, we are therefore in the presence of a genetic disorder suspicion. Given the patient medical history and the successive evolution of the state, we are suspecting congenital hypoparathyroidism versus congenital pseudohypoparathyroidism, which is why PTH is measured - with normal levels, therefore congenital pseudohypoparathyroidism remaining the integration diagnosis.

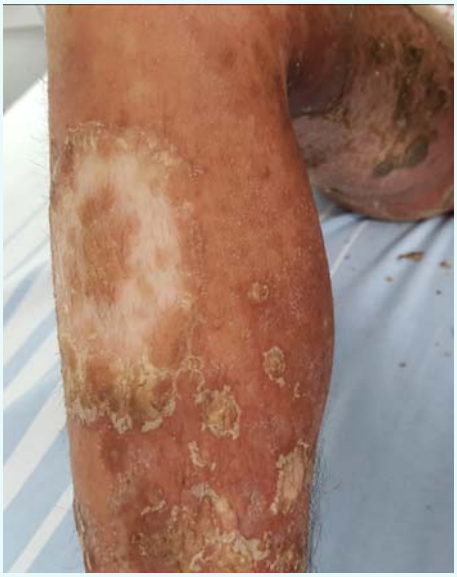
During the admission the patient received intravenous treatment with calcium gluconate and magnesium sulphate, with partial correction, calcium levels rising up to 7,6 mg/dl. At the same time an improvement of the muscle strength is noted, with a decrease of LDH and CK levels, improvement of tendinitis through a decrease of muscle rigidity and improvement of FEVS, previously mentioned. The patient is on her way to Parhon Hospital for genetic tests. A rapid surgical intervention for cataract is necessary; also, the patient requires a permanent caregiver at home.

Discussion

Congenital hypoparathyroidism is the cause of birth defects associated with abnormal development of parathyroid gland, as well as with synthesis or faulty secretion of PTH. Clinical signs are the ones of hypocalcaemia and they can be acute, from tetany (paraesthesia, muscular spasms, Trousseau sign, Cvostek sign, to more severe forms, with seizures, laryngospasm and bronchospasm), cardiac (QT prolongation, hypotension, heart failure, arrhythmia), or chronic, like ectopic calcifications (in basal ganglia), extrapyramidal signs, parkinsonism, dementia, subcapsular cataract, abnormal dentition and dry skin[1,2].

The main paraclinical test for these patients is represented by hypocalcaemia, with low or normal PTH levels. The laboratory tests are usually used to diagnose hypoparathyroidism. The genetic disorder needs to be demonstrated through genetic tests.

Therapeutic management implies administration of calcium with vitamin D long term, with the majority of patients needing these to be administered for their entire lives[3]. The purpose of the treatment is to improve symptoms and to rise and maintain normal calcium levels, with periodic monitoring of calcium levels until a stable serum concentration is established. Daily dose of calcium for children is from 25 to 50



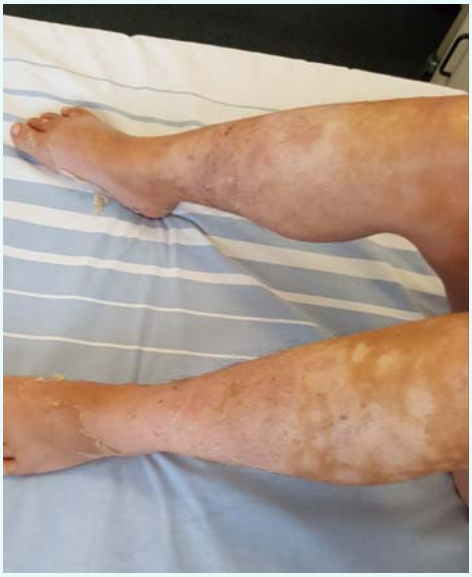
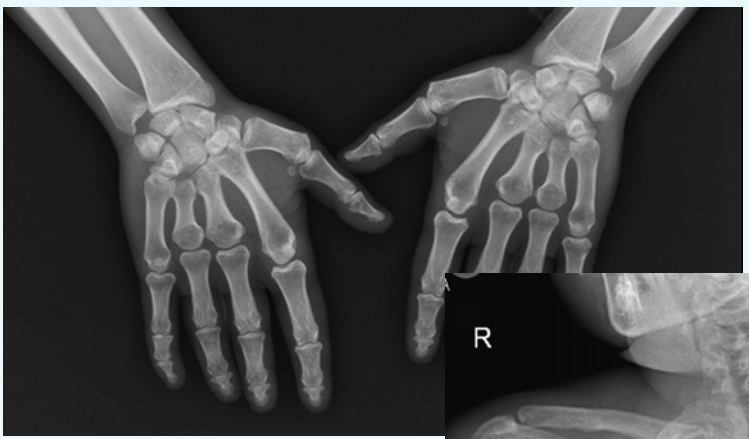


Figure 1. *Skin with erythematous lesions evolved into placards, with intense generalised epidermal peeling at the time of the admission*
Figure 2. *Improvement of the lesions after dermatological treatment*



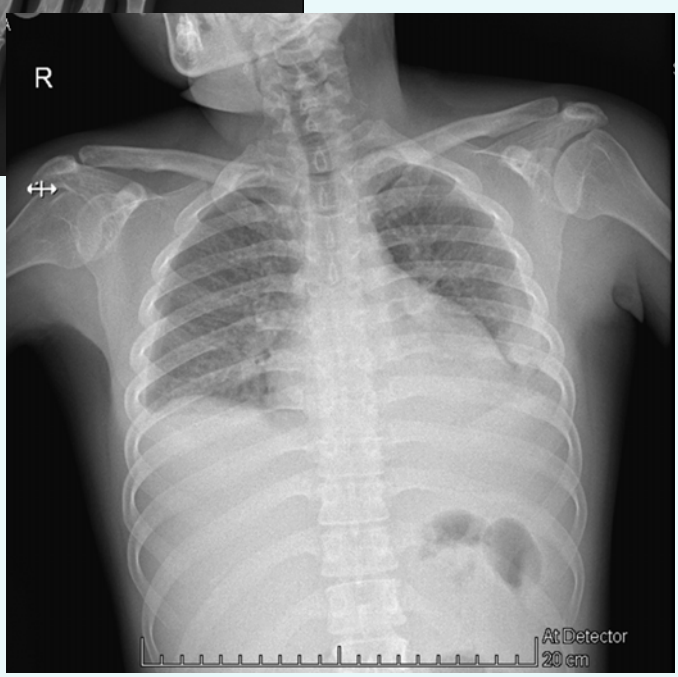


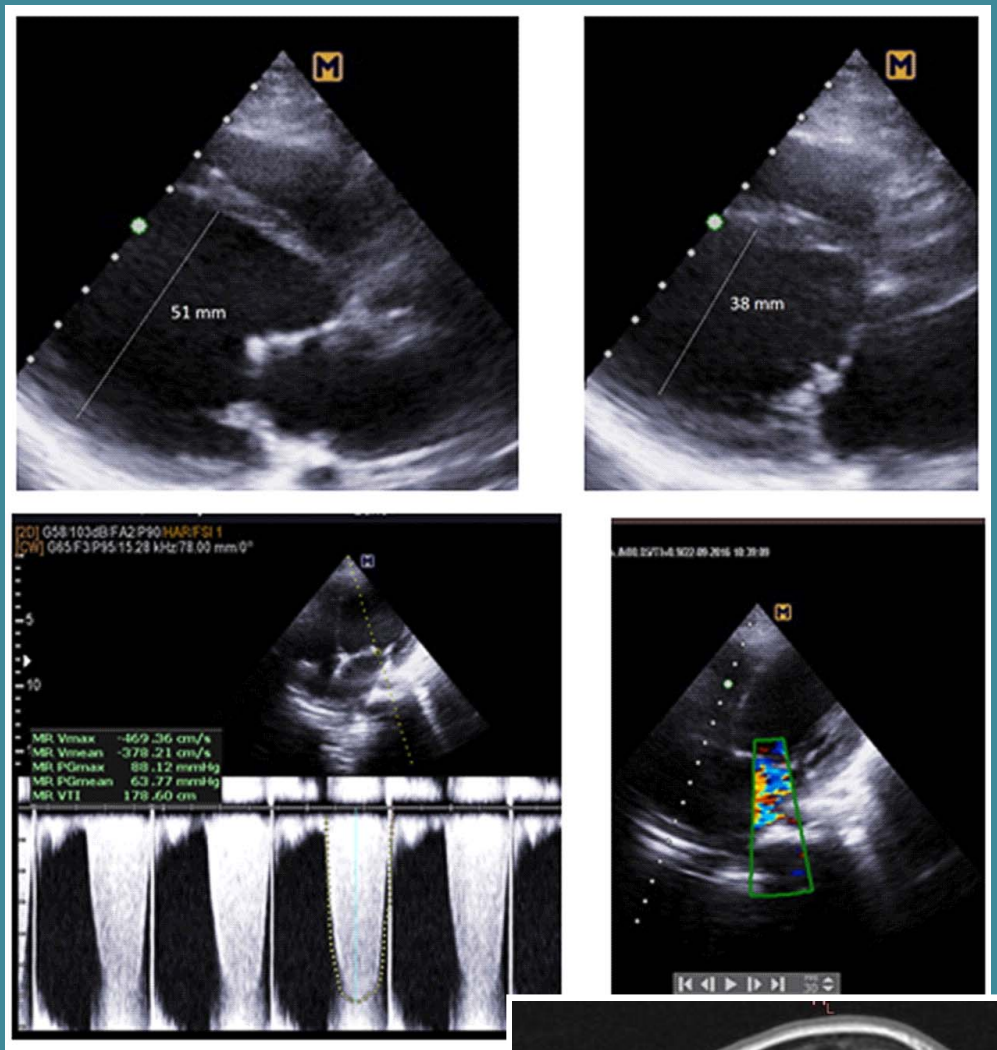
Figure 3. *The hand radiography that shows the hypoplastic aspect of metacarpal bones III and IV bilateral*
Figure 4. *Thoracic X-ray that shows increased diameters of the heart*

mg/kg (1-2 g/day), in divided doses, and doses of 2 mcg/day of vitamin D have to be administered. For adults, the doses are similar[3]. In some patients, when the optimal dosage cannot be maintained, recombinant human parathyroid hormone administration can be considered. However, the efficacy of long term PTH administration was not yet demonstrated[4,5]. Congenital hypoparathyroidism is part of a heterogeneous diseases group, defined by the lack of target organs' (kidneys and sometimes bone) response to PTH, and it is characterised by hypocalcaemia and high serum levels of parathyroid hormone. There are two types of genetic syndromes: pseudohypoparathyroidism type I, characterised by the inability to activate adenylate cyclase to bind Gα protein to the PTH receptor, therefore with no response to hormone administration and low urinary cAMP. In pseudohypoparathyroidism type II, the activation of adenylate cyclase to Gα protein of the PTH receptor is present, with response to hormone and normal or high urinary cAMP (Figure 7).

Pseudohypoparathyroidism type I includes three subgroups: Ia - autosomal dominant disease, characterised by GNAS1 gene mutation (Figure 8), that leads to the inability of activation of adenylate cyclase to PTH receptor[6]. Patients with type Ia and the impairment of this gene, present resistance to other hormones that are coupled with G protein, like TSH, LH, FSH[7]. Patients with this disorder have a number of clinical signs, grouped under the name of Albright hereditary osteodystrophy, that includes round facies, short stature, the shortening of metacarpal joint IV, obesity, subcutaneous calcification and developmental delay[8]. Type Ib is characterised by hypocalcaemia, but without Albright dystrophy specific clinical signs. PTH resistance is present in the kidney and leads to hypocalcaemia, hyperphosphoremia and secondary hyperparathyroidism[9]. Type Ic refers to a mutation subgroup which affects the coupling of G protein with PTH receptor. The ability to stimulate adenylate cyclase is intact, but it no longer binds to PTH through its receptor[10]. Long term treatment of hypocalcaemia secondary to congenital pseudohypoparathyroidism is similar to the one of hypoparathyroidism forms. The purpose of the treatment is to maintain normal calcaemic levels, with 1-2 g calcium/day, in divided doses. The initial dose of calcitriol is 0,25 mcg, twice per day, increased weekly up to the maximum dose of 2 mcg/day[11].

Conclusions

After genetic tests performed at National Institute of Endocrinology „CI Parhon", it was demonstrated that the patient had the



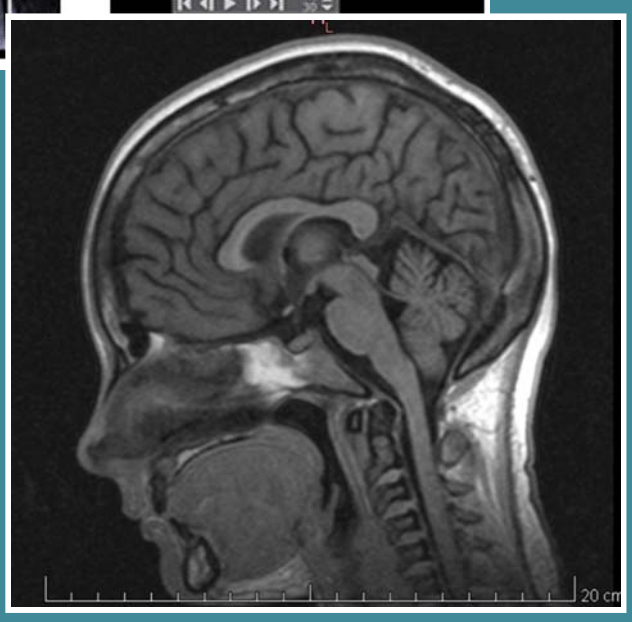


Figure 5. *Echocardiography*
Figure 6. *Cerebral IRM within normal range*

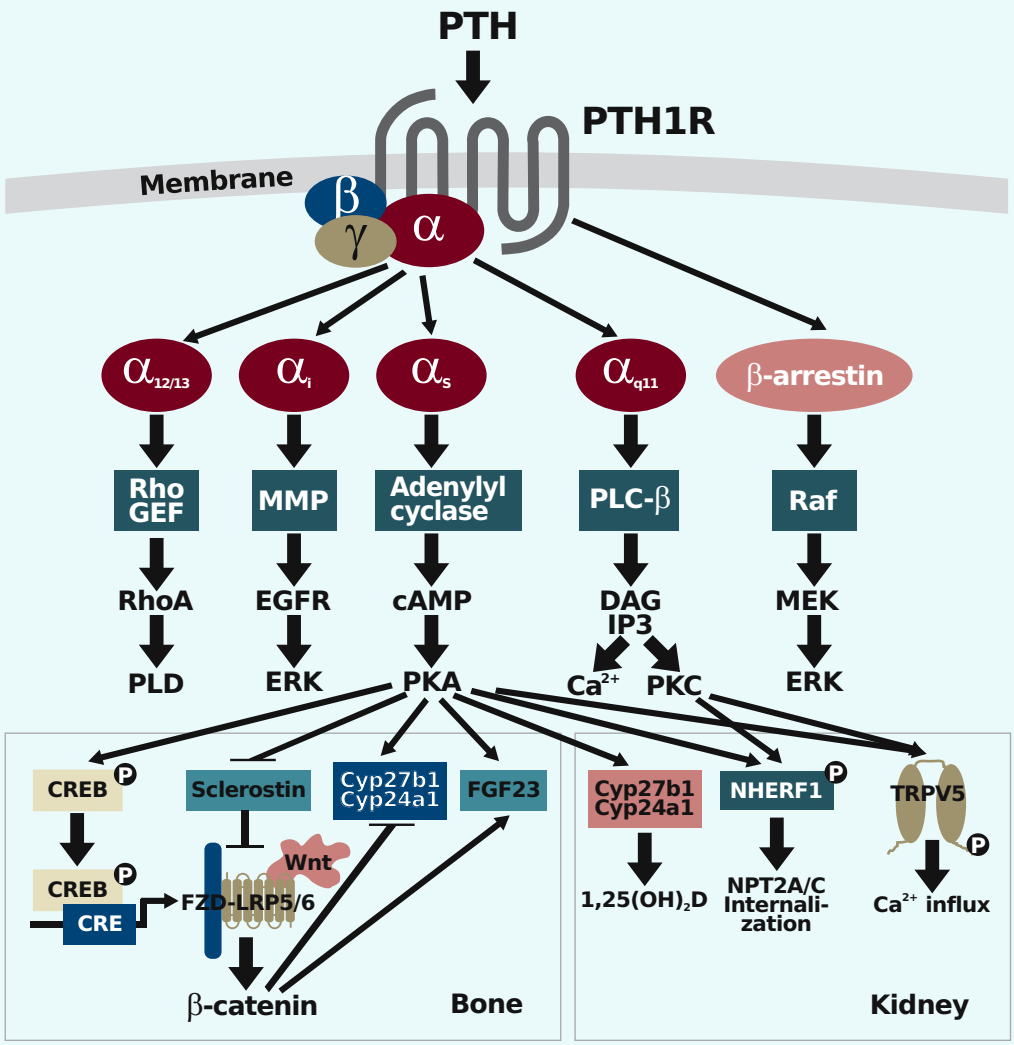


Figure 7. *Activation pathways through G protein to PTH binding*
Cited from Bastepe, Murat, Serap Turan, and Qing He. "Heterotrimeric G proteins in the control of parathyroid hormone actions". Journal of Molecular Endocrinology 58.4: R203-R224. https://doi.org/10.1530/JME-16-0221

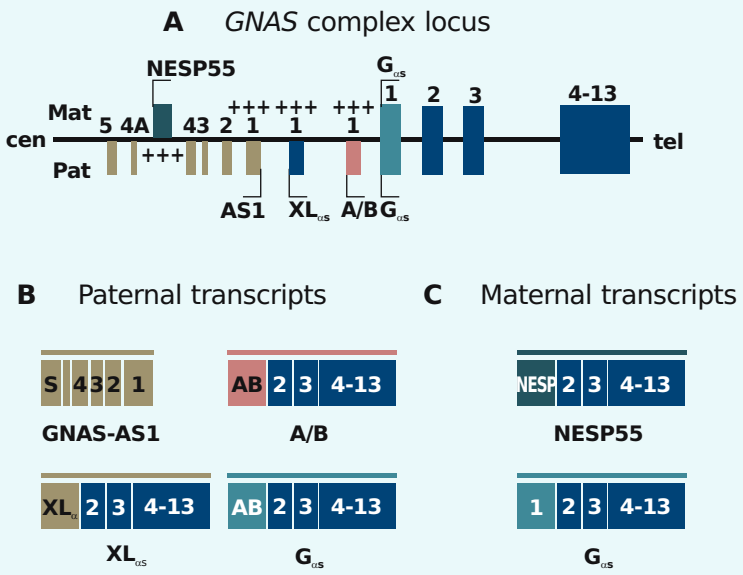


Figure 8. *GNAS complex and genes*
Cited from Bastepe, Murat, Serap Turan, and Qing He. "Heterotrimeric G proteins in the control of parathyroid hormone actions". Journal of Molecular Endocrinology 58.4: R203-R224. https://doi.org/10.1530/JME-16-0221

mutation of the GNAS1 gene, with type Ia of congenital hypoparathyroidism, through TSH resistance. Therefore, the therapeutic regimen at discharge was the following: Levotiroxine 25 µg, 1cp/day, Alpha D_3 0,5 mcg, 1 tablet/day, Lactic calcium 500 mg, the maximum dose of 4 tablets/day, Carvedilol 6,25 mg – ½ tablets twice/day, Spironolactone 25 mg, 1 tablet/day and Digoxin 25 mcg – ½ tablets/day, for heart failure treatment and prevention of recurrence, Levetiracetam 500 mg – tablet/day, Oxcarbazepine 300 mg – 1 tablet/day, for the prevention of seizures.

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