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A Case of delayed diagnosis of Pseudohypoparathyroidism

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Pseudohypoparathyroidism (PHP) is an extremely rare condition. It is a heterogeneous group of disorders characterized by hypocalcaemia, hyperphosphatemia, increased serum concentration of parathyroid hormone (PTH), and insensitivity to the biologic activity of PTH. Different variants have been identified based on molecular defects in the gene GNAS1 (1) encoding the alpha subunit of the stimulatory G protein (Gsa). Here we report a gentleman with the condition.

Case Study

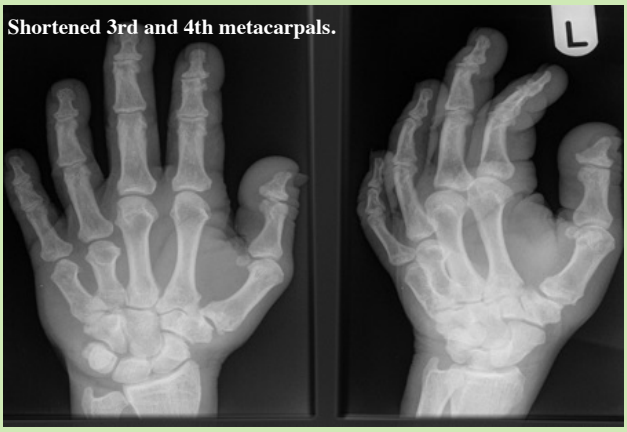
A 65year old, Caucasian gentleman was admitted with weight loss and generally feeling unwell. He had a background history of transitional cell carcinoma of bladder, Hypertension, COPD, Sleep Apnoea, Depression, severe axonal sensory motor peripheral neuropathy, CVA and spinal surgery with internal fixation with rods and bone graft.

X ray chest done a week before admission as part of routine investigation for weight loss by the General Practitioner, showed healing rib fractures with diffuse sclerosis. Malignancy was initially suspected due to the bony changes in the chest X- ray. Hence a full body CT scan was done and was normal.

Incidentally he was noted to have low adjusted calcium of 2.16mmol/L (2.20-2.60), raised Parathyroid hormone (PTH) at 1189ng/L (914-72), raised Alkaline phosphatase (ALP) at 1189u/L (40-130) and low 25-Hydroxy Vitamin D of 15 mmol/L (24-167), consistent with Vitamin D deficiency. He did not have any symptoms of hypocalcemia such as perioral paraesthesia, numbness/tingling in the fingers or muscle cramps.

He was treated with high dose vitamin D replacement of 20,000IU capsule once a week and calcium carbonate 1.5gm tablet twice a day for 8 weeks. X-ray of his hands revealed evidence of short 3rd and 4th metacarpals of both hands. Significantly raised PTH levels could not be explained by Vitamin D deficiency alone; hence PHP was also suspected based on the clinical finding of the 3rd and 4th metacarpals. No other causes of shortened 3rd and 4th metacarpals like Homocysinuria, Turners syndrome, Sickle cell disease, Langer-Giedion syndrome were suspected.

Once he was Vitamin D replete he received maintenance dose of calcium carbonate 1.5 g (calcium 600 mg or Ca2+ 15 mmol) and colecalciferol 10 micrograms (400 units) in the form of Adcal D3 one tablet daily. He has been asymptomatic and normocalcemic on maintenance dose.



Shortened 3rd and 4th metacarpals.

Discussion

PHP is a very rare condition and often diagnosis is missed or delayed due to absence of typical physical signs and biochemical features mimicking vitamin D deficiency. It remains a diagnostic challenge. Signs and symptoms vary from person to person. Calcium is mobilized from the bone and hence patients remain relatively asymptomatic. Our patient was minimally affected by the biochemical abnormality and was in his mid-sixties when a diagnosis of PHP made.

PHP is subdivided into several different types like - Ia, Ib, Ic, type II. Cases of PHP were first reported by Albright in 1942(2). PHP type 1a is the best understood of the different types. The typical features described by Albright includes short stature, rounded face, brachydactyly, dental hypoplasia and soft tissue calcifications termed as “Albright's hereditary osteodystrophy” (3). It is more common in females than males. Diagnosis is usually done by correlating the biochemical results and physical signs. Analysis of the gene GNAS1 helps to identify genetic defect in the type 1a patients.

Type Ia is the most common type and there is family history of genetic defects with typical physical signs of “Albrights hereditary osteodystrophy”, there might be a autosomal dominant pattern (4). Type Ib involves resistance to PTH only in the kidneys. Calcium in the blood is low, but there are no symptoms of Albright hereditary osteodystrophy. Type II pseudohypoparathyroidism also involves low blood calcium and high blood phosphate levels in the absence of physical signs of Type 1a, there is a normal cAMP response to PTH stimulation despite the inherent abnormality in calcium regulation(5).

The goals of pharmacotherapy are to correct calcium deficiency, to prevent complications, and to reduce morbidity. Intravenous calcium is the initial treatment for all patients with severe symptomatic hypocalcemia. Administration of oral calcium and 1alpha-hydroxylated vitamin D metabolites, such as calcitriol, remains the mainstay of treatment and should be initiated in every patient with a diagnosis of PHP. Aim of therapy is to maintain serum total and ionized calcium levels within the reference range, supress PTH levels to normal range and avoiding development of hypercalciuria, as well as regular monitoring. If the serum phosphate levels are high, then diet with low phosphorus is suggested and rarely phosphate binders are used as treatment.

Learning Points

- Interpreting the biochemical results appropriately and if in doubt to seek expert help.
- Thorough physical examination looking for subtle signs and proper record of past medical history.

References

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