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PRIMARY HYPERPARATHYROIDISM – CASE SERIES AND CHALLENGES OF MANAGEMENT IN NIGERIA AND LOW-INCOME COUNTRIES.

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Article Info

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Abstract

Primary hyperparathyroidism (PHPT) is a rare endocrine disorder in which hypercalcemia is documented. They do not produce compressive symptoms, present usually with nonspecific symptoms or may be asymptomatic. The objective of this report is to draw attention to this disorder said to be rare especially in the low- and middle-income countries where PHPT diagnosis is made late when skeletal and renal complications have occurred. Two post-menopausal Nigerian women with a diagnosis of PHPT made in the USA were referred to our endocrine practice in Aba, Nigeria. The older patient opted out of surgery while the younger patient had a successful parathyroidectomy in USA. There is a concern about other women/patients out there who may have PHPT but do not have access to medical services in USA and the developed world. There is, therefore, a need for a high index of suspicion by healthcare professionals and good laboratory support services in Nigeria and similar countries to clinch the diagnosis of PHPT before target organ damages (fractures, kidney stones and kidney failures) start manifesting.

Keywords: primary hyperparathyroidism, challenges of diagnosis and management, low- and middle-income countries, Nigeria.

Introduction:

Primary hyperparathyroidism is a rare endocrine disorder in which there is hypercalcemia in the presence of raised parathyroid hormone (PTH) or inappropriately normal PTH.[1] Hypercalcemia is documented in patients with classical PHPT. The aetiology of PHPT is a single-gland adenoma in majority of the cases (~85%), followed by 4- gland hyperplasia (~14%) and rarely carcinoma (< 1%), therefore, PHPT does not produce compressive symptoms. It could occur spontaneously or as part of multiple endocrine neoplasia (MEN) 1 or 2. PHPT is 3 – 4 times more in women than men and is predominantly a disease of postmenopausal women. [2]

Differential diagnosis of PHPT include familial hypocalciuric hypercalcemia and use of drugs such as hydrochlorothiazides and lithium.[1] Today, surgery is the only curative option but those that do not have surgery are managed by active monitoring/surveillance.[3] Some studies suggest

that these patients on active surveillance over time might experience disease progression or develop complications such as osteoporosis, cardiovascular disease, or renal calculi.[4-7] Other patients are unable to undergo surgery due to co-morbidity or fear of complications. Bisphosphonates improved bone mineral density (BMD) while cinacalcet had no effect on BMD. Cinacalcet maintained its lowering effect on serum calcium over time.[8]

PHPT classically targets the skeleton and the kidneys. In developed countries with routine multichannel biochemical screening, PHPT is usually diagnosed by routine biochemical screening. In low- and middle-income countries, it presents as a symptomatic disease with renal and skeletal complications.[9] PHPT is associated with cardiovascular diseases, gastrointestinal symptoms, cognitive changes and depression.

There is a dearth of published reports on PHPT in asymptomatic patients or patients with non specific symptoms in Nigeria. With two cases presenting to us at Abia State University Teaching Hospital (ABSUTH), Aba, Nigeria less than 4 weeks apart, we, therefore, set out to draw the attention of the medical and scientific community to this endocrine disorder that may not really be rare especially in the low- and middle-income countries. They may, at best, be under diagnosed or underreported in these countries because PHPT usually present with nonspecific symptoms or may be asymptomatic thereby posing significant challenges to their diagnosis and management. This informed our decision to report these two cases and discuss issues in the management of PHPT in Nigeria and other low- and middle-income countries.

Cases 1 and 2:

Two postmenopausal women with a diagnosis of PHPT, each made in the USA, were referred to our endocrine practice in ABSUTH, Aba, Nigeria. Mrs KU, aged 52 years, presented on 20th March 2019 while Mrs CM, aged 70 years, presented on 15th April 2019. Both were asymptomatic prior to diagnosis except for probable menopausal symptoms in the younger lady. Both women were not known to have hypertension and they were not living with DM. They had no drug history of use of lithium or hydrochlorothiazide in the past. Their past medical and family history plus physical examinations were not remarkable.

Their multichannel biochemical screening investigation results done in USA (table 1) shows hypercalcemia and increased intact parathyroid hormone. Mrs CM, the older patient, opted out of surgery and is on 35mg weekly Risedronate orally, calcium and vitamin D supplementation while Mrs KU had a successful parathyroidectomy in USA. Both are being followed up by our team

Table 1: Relevant laboratory results of the 2 patients

Mrs KU	Mrs CM
Na=138mmol/L (135-146)	Na=140mmol/L (135-146)
K=4.1mmol/L (3.5=5.3)	K=4.3mmol/L (3.5=5.3)
Cl=98mmol/L (98-110)	Cl=107mmol/L (98-110)
CO2=26mmol/L (24-30)	CO2=27mmol/L (24-30)
BUN=15mg/dl (8-24)	BUN=17mg/dl (8-24)
Creatinine=0.90mg/dl (0.5-1.5)	Creatinine=0.80mg/dl (0.5-1.5)
Total Ca=11.5mg/dl (8.5-10.5)	Total Ca=11.1mg/dl (8.5-10.5)
Total protein=7.4gm/dl (6.0-8.3)	Total protein=7.1gm/dl (6.0-8.3)
Albumin=4.6gm/dl (3.5-5.0)	Albumin=4.3gm/dl (3.5-5.0)
eGFR > 60ml/min (MDRD)	eGFR > 60ml/min (MDRD)
Intact PTH=129pg/ml (12-72)	Intact PTH=124pg/ml (12-72)

Keyword: eGFR= estimated glomerular filteration rate, PTH= parathyroid hormone

Discussion:

PHPT classically targets the skeleton and the kidneys.[9] In developed countries with routine multichannel screening, PHPT is usually diagnosed by routine biochemical screening in the absence of any specific symptoms. In low- and middle-income countries, it presents as a symptomatic disease when renal and skeletal complications in the form of nephrolithiasis, nephrocalcinosis, chronic kidney disease or pathological fractures are

present. The index cases did not have symptoms of skeletal or renal complications when they were subjected to multichannel screening and found to have PHPT. The implication of not doing routine multichannel screening of all medical cases in Nigeria and other low-income countries is that many patients who have PHPT remain undiagnosed until they present with the renal or skeletal complications of PHPT. Another implication of the under-diagnosis is that the medical community may, falsely, be laying claim that PHPT is a rare endocrine disorder. Both index cases were postmenopausal and other features that may suggest MEN 1 or 2 were absent in them.

Diagnosis of PHPT is based on a finding of increased serum calcium and serum intact PTH or inappropriately normal PTH. Diagnosis of PHPT in our two patients was based on hypercalcemia and high intact PTH. It was made in the absence of specific symptoms of PHPT. Serum Calcium Creatinine Clearance Ratio (CaCrCR) should have been checked while evaluating for PHPT. This is to exclude familial hypocalciuric hypercalcemia (FHH) in which there is mild hypercalcemia and the CaCrCR is <0.01. Familial hypocalciuric hypercalcemia [1] is due to a mutation of the calcium sensor receptor gene (CaSR) gene in the kidney and not due to PHPT. Patients that have FHH do not benefit from surgery (parathyroidectomy).

The younger patient in our report had series of parathyroid imaging studies in the USA including 99Tc sestamibi scintigraphy, ultrasound and computed tomography scans to localize the parathyroid lesions responsible for the PHPT. This was because she planned to have surgery and not as a diagnostic procedure. The older patient in this study opted out of surgery and did not do imaging studies to localize the parathyroid lesions. Surgery (parathyroidectomy) by an experienced surgeon achieves up to 95% cure rate in a single adenoma and indications for parathyroidectomy include symptomatic patients, asymptomatic patients who meet the guideline criteria and those who do not meet the criteria but choose to and have no contraindications. [3] Our younger patient in this case series was asymptomatic but met the guideline criteria for surgery.

Parathyroidectomy in symptomatic patients causes relief of hypercalcemic symptoms, improvement of skeletal and renal health [3] In asymptomatic patients like the younger patient in our series, it corrects the underlying abnormality, improves bone mineral density (BMD), lowers bone turnover and decreases fracture risks.

Guideline criteria [3] for surgery on asymptomatic patients with PHPT include age <50 years, serum Ca above the normal range by >1mg/dl, presence of osteoporosis (BMD T score ≤ -2.5 at the lumbar spine, femoral neck, total hip or distal 1/3 of radius for postmenopausal women or males >50 years), eGFR < 60ml/min, presence of renal stones or nephrocalcinosis. Old patients > 50 years can do surgery if medically stable with no contraindication for surgery or the benefits of surgery outweigh the risks. Asymptomatic PHPT patients who do not meet the guidelines criteria for surgery or are unable or unwilling to undergo parathyroidectomy should have active surveillance or monitoring.[3] Our second patient in this series who opted out of surgery qualified for active monitoring which includes doing BMD assessment every 1 – 2 years and measuring biochemical profile (electrolytes, urea , creatinine, calcium, PTH and Albumin) every year. She is, also, on an antiresorptive agent (bisphosphonate), calcium and vitamin D supplementation.

Finally, the challenges of management of PHPT in Nigeria and other low/middle income countries are enormous. Currently, in Nigeria, multichannel screening of all medical patients is not practiced such that many cases of PHPT may be missed. Sequel to this, diagnoses of PHPT are not made and the healthcare practitioners feel safe to say that PHPT is a RARE ENDOCRINE DISORDER in Nigeria. Secondly, essential imaging studies needed to localize PHPT lesions are not readily available in Nigeria and experienced parathyroid surgeons are extremely scarce. With all these challenges, our patient that had parathroidectomy had to travel back to USA again for the surgery. For patients on active surveillance/monitoring, antiresorptive

agents (bisphosphonates) are expensive and because health insurance scheme is not effective in Nigeria, patients generally pay out of pockets for their medications and periodic investigations. As a result, they are soon lost to clinic follow up and the active monitoring.

Conclusion/Recommendation:

PHPT may not, after all, be a rare endocrine disorder in Nigeria. Under-diagnoses may be responsible for its apparent rarity in Nigeria and other low/middle income countries. There is, therefore, a need to improve the laboratory support services in Nigeria to start doing multichannel biochemical screening of all medical patients. With this, PHPT will become an asymptomatic disease in Nigeria like the rest of USA, Canada and Europe.

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Conflicts of Interest – Nil

Author's contributions:

1. Dr Marcellinus O. Nkpozi - Conception and design of the research with drafting of the manuscript. He, also, takes overall responsibility for the study.
2. Dr Uwa N. Onwuchekwa and Dr Ndukauba Eleweke - Final approval and critical revision of the manuscript