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CASE STUDY

Marijuana-Provoked Hypoprolactinemia and Impaired Bone Mineral Density: Case Report and Review of Literature

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ABSTRACT

Introduction: **The incidence of concurrent hypoprolactinemia and impaired bone mineral density (IBMD) induced by marijuana abuse has not been observed among the general population. To the very best of our knowledge, none of these two rare conditions have previously been documented among Nigerians, within the existing literature.**

Case Report: **Herein, is a rare case of concurrent hypoprolactinemia and IBMD triggered by marijuana abuse, in a 21-year-old undergraduate Nigerian male, who is a regular/heavy marijuana smoker of thirteen months duration. He had presented in our medical facility with complaints of recurrent excruciating lower back pain of three weeks duration which intensified with walking and while undertaking weight-bearing activities. He attested to having and seeking medical attention for, excessive sweating, and insomnia symptoms before the onset of current presenting symptoms. Results of investigations showed positive urine test for marijuana, hypoprolactinemia, distortions of biomarkers of bone metabolism, and radiologic features consistent with IBMD, Having found no other discernible cause of the low back/hip pain and hyoprolactinemia, he was diagnosed clinically with hypoprolactinemia and IBMD secondary to marijuana abuse. This warranted hospital admission where he obtained standardized specialist medical care and was subsequently discharged in good clinical condition with an uneventful follow-up period.**

Conclusion: **This case highlights the dangers of metabolic aberrations due to marijuana abuse and the need to always maintain a high index of suspicion when confronted with it to avoid unnecessary medical protocols.**

Keywords: Hypoprolactinemia, Impaired BMD, Marijuana.

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1. Introduction

Marijuana (cannabis) is one of the most abused illicit substances around the globe and does occupy the number one position as the most common illicit substance of abuse in Nigeria. The abuse of the illicit substance cuts across all genders, ages, and social strata in both developed and developing societies [1], [2]. The trend is more likely to continue with the recent legalization of its use for medical or recreational intents in some countries.

Over the decade, marijuana abuse has been reported in association with several adverse health-related issues including metabolic, mental, physical, and reproductive consequences [1]–[3]. Clinical reports indicate that regular/chronic use of marijuana negatively impacts the endocrinal systems and skeletal structures [1]–[6].

Disorders of prolactin hormone, especially hypoprolactinemia and those of bone mineral metabolism are some of rare metabolic consequences of regular/chronic cannabis abuse documented in previous reports [3]–[6]. However, the concurrence of these two rare marijuana-induced disorders has not been reported before among males within the existing literature.

Herein, we present a rare case of concurrent hypoprolactinemia and impaired bone mineral density (IBMD) triggered by marijuana abuse in a 21-year-old undergraduate Nigerian male.

2. Case Report

A 21-year-old male presented to us, in a stooped position, with lower back pain of three weeks duration. The pain had commenced insidiously without any provoking factors nor trauma, initially of mild degree but has since progressed in severity during the course of the three weeks, radiates to the inner groin, and tends to intensify with walking and minimal weight-bearing activities. He had self-medicated with several analgesics during the three weeks but all to no avail before presenting.

His past medical history had been uneventful except for the fact he reluctantly acknowledged being a heavy/chronic marijuana smoker for thirteen months duration which he occasionally combined with alcohol consumption before the onset of the presenting symptom. He continued marijuana smoking while his symptoms persisted. Three months before the present condition, he had suddenly developed restlessness, excessive sweating, and insomnia which warranted him to seek over-the-counter medications without any significant improvement. He had no family history of any organ disease.

Vital sign evaluation revealed a well-nourished male, well-oriented to place, time, and person but in obvious distress due to pain at the level of lumber region, afebrile with an axillary temperature of 36.9 °C, respiratory rate of 16 cycles/minute, pulse rate of 110 beat/minute (tachycardia), blood pressure of 150/90 mmHg (raised blood pressure) and had mildly dilated pupils. He had a normal configured spine with moderate tenderness over the lumbar spine without any evidence of sensory and motor deficits in the lower extremities. Other major organ systems were normal.

An initial assessment of traumatic lower back pain was made and urgent laboratory investigations and lumbosacral X-ray were requested. He was immediately admitted, immobilized, sedated (IV Diazepam), and under full analgesia (IV Diclofenac) while waiting for the results of the initially requested investigations. Following the review of results from the initial laboratory investigations and that of the lumbosacral X-ray, an urgent request for blood markers for bone metabolism and dual-energy X-ray absorptiometry (DEXA) were requested to explore the possibility of co-existent IBMD.

Based on all the available laboratory and radiological results as shown in Table I, he was finally diagnosed with marijuana-provoked severe hypoprolactinemia associated with IBMD/osteopenia. From day one at admission while under full analgesia, IBMD was managed using daily oral calcium/vitamin D supplements (1000 mg/600 IU) while hypoprolactinemia was managed using oral metoclopramide (10 mg tds). High blood pressure was managed using beta blockers.

During management while on admission, he was monitored using relevant blood parameters on a weekly basis as depicted in Table II for four weeks. He achieved good clinical recovery by the fourth week at admission as evidenced by cessation of all of his symptoms, normalization of vital signs, and normalization of most laboratory parameters except the persistence of mildly reduced serum prolactin levels and radiological features of asymptomatic IBMD. Following expert review, he was discharged home in good clinical status with oral medications but to continue monthly follow-up clinic visits for laboratory evaluation, radiological examinations, and rehabilitative program on substances (Table III).

By the sixth month of follow-up clinic visits, all relevant laboratory parameters had normalized including those of radiological examinations. Due to the clinical/laboratory evidence of full recovery as depicted in Table III, all therapeutic interventions were halted.

However, he continued the monthly follow-up clinic visits for another four months during which he was referred for full-scale marijuana abuse therapy, rehabilitation, counseling, dietary advice, and engagement in regular weight-bearing and aerobic exercises.

3. Discussion

3.1. Key Features

Over the decade, several acute/chronic physical, psychological, mental, and metabolic disorders have been documented in association with marijuana abuse. While very few isolated cases of hypoprolactinemia and IBMD have been documented in association with marijuana abuse in the literature, the concurrence of these two unrelated disorders is rare in the literature and even rarer among males. The current case presented clinical features of these rare disorders supported by laboratory/radiologic evidence (shown in Table I) following heavy/chronic marijuana use. Hence, the case brings to the fore the unpredictability of the deleterious consequences of illicit marijuana abuse.

3.2. Pathogenesis

The exact evolution of hypoprolactinemia and IBMD triggered by marijuana abuse is largely unknown but speculative in the literature. However, several experts have linked these two unrelated disorders to the chronic impact of delta-9-tetrahydrocannabinol (9-THC), the most potent and active component of marijuana, on the endogenous cannabinoid receptors types 1 and 2 (CB1R & CB2R). Thus, 9-THC tends to mimic the actions of the naturally-occurring cannabinoids called endocannabinoids [3]. Marijuana-induced hypoprolactinemia has been linked to enhanced dopamine (DA) secretion, as observed in the index case, due to the chronic effect of 9-THC on the hypothalamic CB1R. CB1R is co-localized with DA receptors in hypothalamic DA projections and 9-THC acutely increases the release of DA [3]. DA exerts feedback inhibition by stimulating the naturally-occurring endocannabinoid secretion which then inhibits further DA release. However, with chronic exposure to 9-THC as in the index case, there is down-regulation of the CB1R, which interferes with this feedback process, resulting in exaggerated DA secretion. This consequently results in prolactin suppression leading hypoprolactinemia [3].

As also observed in the index case, heavy/chronic marijuana use is a potential cause of low bone mineral density, increased bone turnover, and predisposition to fractures in previous reports [3], [4]. However, the underlying mechanism is still also speculative. CB1R and CB2R are also expressed in the skeletal system and their activation by

TABLE I: Results of Initial Laboratory/Radiological Investigations

Investigation/Reporting units	Normal values/Reference interval	Results of investigations	Remark/Interpretation
Blood (plasmalserum) parameters			
Sodium, mmol/L	135–145	138.0	Normal
Potassium, mmol/L	3.6–5.2	3.90	Normal
Bicarbonate, mmol/L	22–32	25.0	Normal
Chloride, mmol/L	96–106	98.70	Normal
Creatinine, μmol/L	70–115	80.20	Normal
Urea, mmol/L	2.1–7.1	3.60	Normal
Glucose, mmol/L (random)	<7.8	4.90	Normal
Total calcium, mmol/L	2.2–2.6	2.30	Normal
Inorganic phosphate, mmol/L	0.81–1.45	0.90	Normal
Magnesium, mmol/L	0.7–1.7	1.10	Normal
PTH, ng/L (Intact)	10.0–65.0	21.30	Normal
25(OH)$_2$ D, nmol/L	25.0–162.0	25.40	Normal
PINP, ug|L	***22.0–87.0***	***151.40***	***Increased***
CTX, ug|L	***60.0–700.0***	***863.20***	***Increased***
Osteocalcin, µg|L	***3.0–13.0***	***26.60***	***Increased***
Total protein, g/L	60.0–80.0	67.20	Normal
Albumin, g/L	35–55	40.00	Normal
AST activity, IU/L	<48	20.10	Normal
ALT activity, IU/L	<55	23.40	Normal
ALP activity, IU/L	**56–128**	**204.0**	**Increased**
Total bilirubin, μmol/L	0.0–34.0	11.70	Normal
Conjugated bilirubin, μmol/L	0.0–3.4	0.90	Normal
Cortisol, nmol/L (8 am–9 am)	138.0–635.0	144.50	Normal
Growth hormone, μg/L (basal)	2.0–5.0	2.70	Normal
Insulin-like growth factor-1, μg/L	202.0–433.0	267.90	Normal
Thyroid-stimulating hormone, mIU/L	0.0–4.2	2.30	Normal
Free T4, pmol/L	10.3–34.7	16.70	Normal
Free T3, pmol/L	3.2–6.8	3.90	Normal
Follicle-stimulating hormone, IU.L	1.4–15.4	3.10	Normal
Luteinizing hormone, IU/L	1.2–7.8	2.10	Normal
Testosterone, nmol/L	9.0–34.70	10.90	Normal
Prolactin, µg|L	***3.0–14.7***	***0.50***	***Markedly reduced***
D-dimer, μg/L	<500	176.3	Normal
Troponin 1, ng/L	0.0–40.0	5.90	Normal
C-reactive protein, nmol//L	<47.6	34.40	Normal
Serotonin, nmol|L	***170.0–1,140.0***	***62.50***	***Markedly decreased***
Dopamine, pmol|L, supine (30 minutes)	***0.0–475.0***	***884.60***	***Increased***
Norepinephrine, pmol|L, supine (30 minutes)	***650.0–2,423.0***	***4,665.0***	***Increased***
Urine analysis parameters			
Protein, g/L (random)	0.0–0.15 g/L	0.10	Normal
Glucose, mmol/L (random)	0.0–0.8	0.40	Normal
24-hour urinary calcium excretion, 24-hour urinary phosphate excretion, Urine drug test (random)	—	Positive for marijuana; negative for others**	Marijuana positive
Radiological parameters			
Plain X-ray of the Lumbosacral region	—	*Altered trabecular pattern, cortical thinning, and increased radiolucency.*	*Features suggestive of osteopenia.*
DEXA scan (lumber spine/femoral neck/total hip)	*T-score >-1*	*Nil evidence of fracture* *T-score: −2.10* *Nil evidence of fracture*	*DEXA scan suggested.* *Confirmed IBMD/ Osteopenia*

Notes: PTH: parathyroid hormone; 25(OH)$_2$ D: 25-hydroxyvitamin D; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; PINP: N-terminal pro-peptide of type 1 pro-collagen; CTX: C-terminal telo-peptide of type 1 collagen; DEXA: dual-energy x-ray absorptiometry; **others: cocaine, opioids, alcohol, etc; IBMD: impaired bone mineral densitys.

TABLE II: Weekly Trend of Results of Relevant Laboratory/Radiological Investigations While on Admissions

Investigation/Reporting units	Baseline results	Week 1 result	Week 2 result	Week 3 result	Week 4 result	Remark
Blood (plasmalserum) parameters						
Total calcium, mmol/L	2.30	2.30	2.34	2.35	2.35	Normal
Inorganic phosphate, mmol/L	0.90	0.90	1.00	1.10	1.10	Normal
Magnesium, mmol/L	1.10	1.10	1.20	1.20	1.30	Normal
PTH, ng/L (Intact)	21.3	21.4	22.3	22.4	22.0	Normal
$25(OH)_2$ D, nmol/L	25.4	26.5	27.8	28.6	30.7	Normal
PINP, ug/L	151.4	145.1	110.6	89.5	66.6	Normalized
CTX, ug/L	863.2	804.3	710.9	623.4	366.7	Normalized
Osteocalcin, μg/L	26.6	23.9	16.3	11.6	7.8	Normalized
ALP activity, IU/L	204.0	189.0	136.0	121.0	88.0	Normalized
Prolactin, µg/L	***0.50***	***1.30***	***2.60***	***3.30***	***4.20***	***Mildly reduced***
Serotonin, nmol/L	102.5	123.4	267.8	390.7	552.3	Normalized
Dopamine, pmol/L, supine (30 minutes)	884.6	712.8	521.1	393.4	286.5	Normalized
Norepinephrine, pmol/L, supine (30 minutes)	4,665.0	2,445.0	2,011.3	1,170.6	781.2	Normalized
Epinephrine, pmol/L, supine (30 minutes)	487.9	345.0	232.4	176.8	114.6	Normalized

Notes: PTH: parathyroid hormone; $25(OH)_2$ D: 25-hydroxyvitamin D; PINP: N-terminal pro-peptide of type 1 pro-collagen; CTX: C-terminal telopeptide of type 1 collagen; DEXA: dual-energy x-ray absorptiometry.

the naturally-occurring endocannabinoids, which have full agonist activities at these receptors, modulates metabolic bone activities in favor of bone growth and remodeling [7]–[10]. CB1R is abundantly present mainly in skeletal sympathetic nerve terminals, thus regulating the adrenergic tonic restrain of bone formation, as increased sympathetic activities with enhanced norepinephrine release inhibit osteoblastic activities/bone formation as also observed in the index case [7], [10].

CB2R is abundantly expressed in osteoblasts/osteoclasts, stimulates bone formation, and inhibits bone resorptive activities. Unlike the naturally-occurring endocannabinoids, 9-THC is a partial agonist at the CB1R and CB2R [9], [10]. Hence, some research findings suggest that with heavy/chronic exposure to 9-THC, as observed in the index case, 9-THC tend to act as an antagonist at the CB1R/CB2R, inhibiting the endocannabinoids [8], [9], and limiting their beneficial activities in bone growth and remodeling activities. Furthermore, 9-THC has great affinity and potency at the CB1R than the CB2R. It has also been speculated that with heavy/chronic exposure of 9-THC on the CB1R, 9-THC could act as a full agonist at the CB1R, enhancing the release of norepinephrine from the sympathetic terminals which tend to inhibit osteoblastic activities [8]–[10]. This may also explain the exaggerated and heightened plasma norepinephrine concentration observed in the index case (see Table I).

3.3. *Clinical Features*

In males, hypoprolactinemia has been associated with several metabolic, psychological, anxiety, reproductive, and sexual disorders/dysfunctions [11], [12]. However, the index case presented only anxiety disorders (restlessness, excessive sweating, and insomnia) [12]. Chronic exposure to 9-THC enhances secretion of the catecholamine (norepinephrine/dopamine) while inhibiting serotonin reuptake in nervous tissues, and therefore, reducing blood serotonin concentration as observed in the index case [13]. Hence, it has been speculated that while hyperactivity of the dopaminergic system could account for some of the anxiety features observed in hypoprolactinemia, the hyposerotonergic tone fits well with these anxiety-associated clinical features frequent in hypoprolactinemic cases, as was also observed in the index case [14]. The index case presented with back pain which is an unusual feature of osteopenia. This brings to the fore the need to entertain a high index of clinical suspicion when challenged with a similar case.

3.4. *Investigations/Diagnosis*

The investigations of hypoprolactinemia include proper/thorough laboratory and radiological evaluation of the endocrine system of suspected cases, in addition to investigating the possible causes, as was done for this index case. The diagnostic guideline for hypoprolactinemia is based on serum prolactin level of less than 5 μg/L in males, which was applied to the index case [11]. The investigation for IBMD is more complicated than that of hypoprolactinemia. This includes both standard radiological (plain X-ray/central DEXA scan) and comprehensive laboratory evaluations of relevant blood and urine parameters. However, the diagnosis of IBMD depends entirely on findings from DEXA using the bone mineral density T-score or the Z-scores.

3.5. *Treatment*

There are very few treatment options for hypoprolactinemia which depends entirely if the etiology is due to reversible or irreversible causes. However, in the index case, the causative agent was reversible which was likely due to exaggerated hypothalamic dopamine suppression of prolactin secretion. Metoclopramide has been successful in ameliorating the dopamine-associated inhibitory effect on prolactin secretion which was an effective agent in the index case [15]. The standard treatment modalities for osteopenia entirely depends on the age and comorbid conditions of the patient. For a young adult as in the index case, this includes adequate calcium/vitamin D replacement and the use of anti-resorptive agents if the patient is at risk of fracture. Hence, due to the low risk of fracture in the

TABLE III: Monthly Trend of Results of Relevant Laboratory/Radiological Investigations Following Discharge from the Hospital

Investigation/ Reporting units	Baseline result	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Remark
Blood (plasmalserum) parameter								
Prolactin, μg/L	2.80	2.83	2.88	2.93	4.34	6.60	7.90	Normalized serum prolactin level
Radiological parameters								
Plain X-ray of the Lumbo-sacral region	Osteopenia	Not done	Not done	Not done	Not done	Not done	Normal features	Normal X-ray findings
DEXA scan (lumber spine/femoral neck/total hip)	T-score: −2.10 (IBMD/ osteopenia)	Not done	Not done	T-score: −1.30 (IBMD/ osteopenia)	Not done	Not done	T-Score: +0.40	Normalized bone mineral density

Note: DEXA: dual-energy x-ray absorptiometry; IBMD: impaired bone mineral density.

index case, we had only calcium/vitamin D supplements that was effective in the index case.

4. Conclusion

Herein, we presented a rare case of concurrent hypoprolactinemia and IBMD triggered by marijuana abuse in a 21-year-old Nigerian male. He had presented with classic features of hypoprolactinemia but an unusual/rare feature of IBMD/osteopenia. He was promptly admitted, investigated/diagnosed based on standard guidelines, clinically managed using standard protocols, discharged with good clinical outcome, and had an uneventful follow-up period. The case highlights the dangers of marijuana abuse and the need for physicians to entertain a high index of suspicion when challenged with a similar case.

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Consent

This was obtained from the patient before this report.

Declaration of Competing Interest

None to declare.

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