

Recurrent Galactorrhoea: A consequence of unheeded primary hypothyroidism

Omokore OA¹, Nwachukwu NO², Fuwape OD¹, Arijeniwa AA², Adekoya AO³, Idowu AO^{1,4}

¹Department of Internal Medicine, Babcock University Teaching Hospital, Ilishan-Remo, Ogun State, Nigeria

²Department of Paediatrics, Babcock University Teaching Hospital, Ilishan-Remo, Ogun State, Nigeria

³Department of Radiology, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Sagamu, Ogun State, Nigeria

⁴Benjamin S Carson School of Medicine, Babcock University, Ilishan-Remo, Ogun State, Nigeria

Submitted: 19th May 2021

Accepted: 19th June 2021

Published: 30th June 2021

Abstract

Background: Primary hypothyroidism can lead to hyperprolactinemia through several mechanisms in both men and women, manifesting as galactorrhoea, loss of libido and infertility in both sexes, as oligomenorrhoea/amenorrhoea in women, and as gynecomastia and erectile dysfunction in men.

Case presentation: Here presented is a 28-year-old Nigerian woman with a history of recurrent bilateral painless galactorrhoea of 12 years' duration and persistent low mood. Physical examination was unremarkable. The hormonal assay revealed elevated thyroid-stimulating hormone, elevated serum prolactin, low thyroxine, and low triiodothyronine levels. Magnetic resonance imaging of the brain revealed normal findings. A diagnosis of hyperprolactinemia secondary to primary hypothyroidism was made. Pharmacological therapy began with thyroid hormone replacement therapy and a dopamine agonist: 75 micrograms of levothyroxine daily and 0.5 micrograms of cabergoline twice weekly for 8 weeks. After 8 weeks of pharmacological therapy, hormonal assay revealed values within the reference range with significant symptomatic improvement evidenced by cessation of galactorrhoea and low mood.

Conclusion: Primary hypothyroidism has been proven to be one of the numerous causes of hyperprolactinemia and it could be unheeded in a patient who does not present with the typical signs and symptoms of primary hypothyroidism.

Keywords: Primary hypothyroidism; hyperprolactinemia; galactorrhoea; thyroid hormone replacement therapy; dopamine agonist; Nigeria.

Background

A plethora of aetiologies can cause hyperprolactinemia. Causes could be physiological, drug-induced, or pathological. Stress, pregnancy, and lactation are physiological causes (1, 2). The use of drugs like antipsychotics, antiemetics, antidepressants, opioids, prokinetics, and estrogen-containing drugs could lead to hyperprolactinemia (1, 3). Pathological causes include prolactinoma and

other masses in the Sella turcica, polycystic ovarian syndrome (PCOS), hypothyroidism and chronic kidney disease, hyperprolactinemia could also be idiopathic (1, 4). Clinching a diagnosis requires thorough history taking, physical examination, and investigations (5).

Symptoms of hyperprolactinemia in female patients include oligomenorrhoea or amenorrhoea, infertility, and galactorrhoea. In men, it could result in gynecomastia, infertility,

Correspondence:

Omokore, Olutomiwa A.

Department of Internal Medicine,

Babcock University Teaching Hospital, Ilishan Remo, Ogun State, Nigeria.

+2349037689291; omokoreolutomiwa@gmail.com

and erectile dysfunction. Hyperprolactinemia could also be an incidental finding without symptoms (6).

Galactorrhoea is one of the commonest presentations in clinical endocrinology with 20-25% of women experiencing galactorrhoea at least once in their lives, and 90% of women with hyperprolactinemia experiencing galactorrhoea (6).

Prolactin, the hormone implicated in hyperprolactinemia is a peptide hormone from the adenohypophysis. It is inhibited by dopamine and stimulated by angiotensin II, antidiuretic hormone, thyrotropin-releasing hormone, oxytocin, and vasoactive intestinal peptide (7).

There is an intricate relationship within the endocrine system, sometimes a change in one axis will cause a change in other(s). One of these relationships is between thyroid hormones and prolactin levels. In hypothyroid patients, a rise in serum prolactin is a result of central (hypothalamic) secretion of thyrotropin-releasing hormone (TRH) leading to the production of thyroid-stimulating hormone (TSH) and prolactin from the anterior pituitary gland. Exceptions include hypothyroidism caused by defects in production, secretion, or action of TRH in which

stimulatory feedback is absent due to deficiency of TRH (8).

Case summary

A 28-year-old Nigerian woman had been receiving management for recurrent galactorrhoea of 12 years in the Gynaecology Clinic. She had been using Cabergoline which she discontinued 3 months before presentation, thus resulting in her recurrent lactation.

There was no history of headaches, blurry vision, early morning projectile vomiting, and seizures.

There was a history of persistent low mood. However, there was no history of cold intolerance, constipation or change in bowel habits, neck swelling, menstrual irregularities, and weight gain. There was no history of voice change or difficulty breathing. There was no history suggestive of the use of Haloperidol and other Tricyclic antidepressants. There was no family history of thyroid disease, autoimmune disease, or hyperprolactinemia. There was no history of cigarette smoking, alcohol use, or use of recreational drugs.

Hormonal assays were ordered from two laboratories and the results are as follows:

Table 1: Hormonal assay results from first laboratory

Hormone	Patient Values	Reference Interval	Unit
LH	9.0	Follicular phase: 1.68 – 15.0 Ovulatory peak: 21.9 – 56.6 Luteal phase: 0.61 – 16.3	mIU/ml
FSH	4.6	Follicular phase: 3.2 – 10.0 Mid cycle peak: 7.5 – 20.0 Luteal phase: 1.3 – 11.0	mIU/ml
Prolactin	221.9	3.8 – 23.2	ng/ml
TSH	42.2	0.4 -6.0	mIU/ml
Free T3	1.2	1.4 – 4.2	pg/ml
Free T4	0.3	0.8 – 2.0	ng/dl

Table 2: Thyroid Function Results from second laboratory

Hormone	Patient Values	Reference Interval	Unit
TSH	40.611	0.380 – 5.330	mIU/L
Free T3	6.61	3.6 – 6.0	pmol/L
Free T4	6.35	7.2 – 16.4	pmol/L

She was then referred to the Endocrinology Unit for further review of the result and expert management, after which a diagnosis of Hyperprolactinaemia secondary to Primary Hypothyroidism was made. She was started on pharmacological therapy with 75µg of

Levothyroxine daily before breakfast and 0.5 µg of Cabergoline twice weekly for 8 weeks.

After 8 weeks of Levothyroxine and Cabergoline use, there was significant symptomatic improvement evidenced by cessation of galactorrhoea and persistent low mood and, her thyroid function test and prolactin assay showed

values within the reference range. The results are as follows:

Table 3: Hormonal Assay Results post-levothyroxine therapy

Hormone	Patient Values	Reference Interval	Unit
Prolactin	18.1	3.8 – 23.2	ng/ml
TSH	2.981	0.380 – 5.330	mIU/L
Free T3	5.32	3.6 – 6.0	pmol/L
Free T4	13.44	7.2 – 16.4	pmol/L

Brain Magnetic Resonance Imaging (MRI) showed:

Figure 1: T1-weighted sagittal view of Brain MRI showing normal-sized pituitary gland (white arrow)

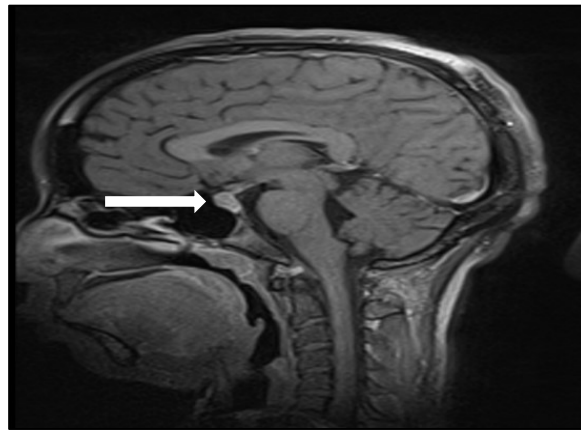
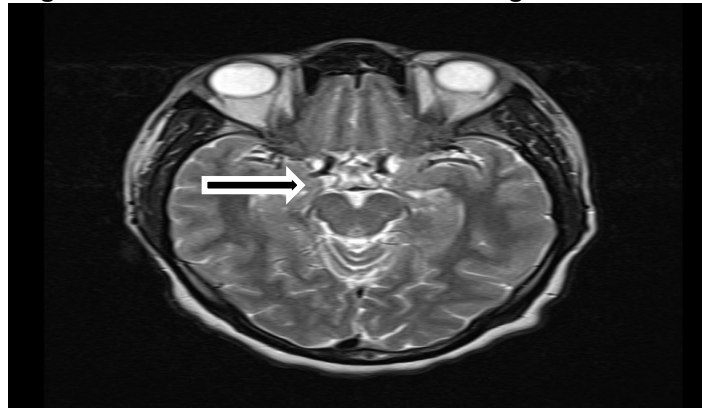


Figure 2 – T1-weighted sagittal view of Brain MRI showing normal-sized pituitary gland (white arrow) [zoomed in]



Figure 3: T1-weighted axial view of Brain MRI showing normal-sized pituitary gland



Pre- and post-contrast MRI of the brain was performed on 1.5 T MRI in multiple planes using T1 & T2 Weighted spin-echo sequence along with fluid-attenuated inversion recovery (FLAIR), gradient recalled echo (GRE), diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) images.

The cerebral parenchyma reveals no other obvious focal or diffuse area of altered signal intensity. The basal ganglia, thalamus brainstem, and cerebellum are normal. The ventricles, cisterns, and sulci are normal.

The pituitary gland is normal in size and signal intensity. Bilateral cavernous sinuses are normal. Both cerebellopontine angle cisterns are unremarkable. The marrow of the cranial vault appears normal. There is no abnormal parenchymal or meningeal enhancement. The intracranial vessels display the expected flow voids. The conclusion is that there was no significant parenchymal abnormality is seen in the brain and pituitary gland.

Discussion

Prolactin is a peptide hormone secreted by the lactotroph cells in the anterior pituitary gland. It stimulates the production of epithelial cells in the breast that produce milk, leading to milk secretion (9). Prolactin secretion is stimulated by thyrotropin-releasing hormone (TRH), vasoactive intestinal peptide, epidermal growth factor, angiotensin II, antidiuretic hormone, oxytocin, and dopamine receptor antagonists (7, 9). Its secretion is inhibited by prolactin inhibitory factors or dopamine (10).

In primary hypothyroidism, the thyroid gland does not secrete adequate amounts of thyroid hormones despite a well-functioning hypothalamus and anterior pituitary gland. The presence of reduced levels of thyroid hormones in the blood increases the secretion of TRH from

the hypothalamus through a loss of thyroxine negative feedback inhibition (11). Therefore, in patients with primary hypothyroidism, there are increased levels of TRH.

Prolactin-producing lactotroph cells contain TRH receptors (12), hence when TRH is elevated in primary hypothyroidism, it also binds to the TRH receptors in lactotrophs and causes the production of prolactin. Hypothyroidism also causes reduced sensitivity to dopamine in lactotroph cells, blocking the inhibition of prolactin secretion by dopamine (13). T3 has been shown to decrease prolactin mRNA levels in lactotroph cells, therefore, hypothyroidism would lead to an increase in the synthesis of prolactin. Prolactin clearance is also reduced in hypothyroidism (11). Primary hypothyroidism can, therefore, result in hyperprolactinemia through any of these mechanisms.

The first time hyperprolactinemia was reported in a patient with subclinical hypothyroidism was in 1988 (14). In a study, the incidence of hypothyroidism in hyperprolactinemia was found to be 25.68% (15).

In a study by Sharma et al, hyperprolactinemia was found to be especially common in patients with TSH > 7.5mIU/l (=50%) (16).⁽¹⁶⁾ TSH was the best predictor of serum prolactin, followed by free T4 (16). It was found that TSH ≥ 7.51 MIU/l in females and ≥ 8.33 MIU/L in males had a sensitivity of $\approx 50\%$ with a very high specificity of $>90\%$ in detecting hyperprolactinemia (16). In another study, the prevalence of hyperprolactinemia in hypothyroid females was found to be 21% (23.07% in clinical hypothyroid females and 17.14% in subclinical hypothyroidism), and the prevalence of galactorrhoea was 1% in subclinical hypothyroid females and 1.53% in clinical hypothyroid females (17).

The patient in this case report had recurrent galactorrhoea for 12 years and had been on treatment with Cabergoline, a potent dopamine D₂ receptor agonist which she discontinued 3 months before presentation. On presentation, she was diagnosed with hypothyroidism, with a reduced level of free T₄ (6.35 pmol/L) and an elevated level of TSH (40.611 mIU/L). However, her only symptom of hypothyroidism was a persistent low mood, which is quite atypical, compared with the classical features of weight gain, cold intolerance, constipation, and menstrual irregularities (18). As a consequence of the untreated hypothyroidism, she developed hyperprolactinemia evidenced by galactorrhoea and prolactin of 221.9ng/ml. There were no other classical features such as irregular menstruation, hirsutism, or infertility (19). Noteworthy is the fact that this patient was not married neither was she trying to conceive a child, so infertility could not be elicited or ascertained. Her brain MRI showed a normal-sized pituitary gland, indicating that hyperprolactinemia can occur without hyperplasia of the pituitary gland.

Upon treatment with Levothyroxine for 8 weeks, her TSH and Prolactin levels were within the reference range - 2.981 mIU/L and 18.0 ng/ml respectively, and there was significant symptomatic improvement evidenced by cessation of the galactorrhoea, further corroborating the direct link between primary hypothyroidism and hyperprolactinemia in this patient. Similar cases have been found where pathological findings receded after thyroid hormone replacement therapy (11, 20, 21).

Study limitations

Thyroid antibodies were not assayed to further determine the possible cause of the hypothyroidism in this patient, due to financial constraints. Further Prolactin assay was not done to ascertain the percentage of Macroprolactin in this patient.

Conclusion

Primary hypothyroidism has been proven to be one of the numerous causes of hyperprolactinemia and it could be unheeded in a patient who does not present with the typical signs and symptoms of primary hypothyroidism. It is, therefore, pertinent for physicians to exhaust the possible aetiologies of hyperprolactinemia before the commencement of symptomatic treatment and/or neurosurgery (22).

Declaration

Ethical consideration

Informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Consent for Publication

The authors hereby give consent for the publication of our work under the creative commons CC Attribution-Non-commercial 4.0 license.

Conflict of interest

The authors have declared that there is no conflict of interest.

Funding

The authors received no funding for this research.

Authors' Contributions

IAO managed the patient, conceived the study, and served as the guarantor. OOO, NNO, FOD, and AAA participated in data collection, manuscript writing, and editing, AAO interpreted the radiology films. All authors read and approved the final manuscript.

References

1. Serri O, Chik CL, Ur E, Ezzat S. Diagnosis and management of hyperprolactinemia. *Cmaj*. 2003 Sep 16;169(6):575-81.
2. Vilar L, Fleseriu M, Bronstein MD. Challenges and pitfalls in the diagnosis of hyperprolactinemia. *Arquivos Brasileiros de Endocrinologia & Metabologia*. 2014 Feb;58(1):9-22. <https://doi.org/10.1590/0004-2730000003002>
3. Vilar L, Abucham J, Albuquerque JL, Araujo LA, Azevedo MF, Boguszewski CL, Casulari LA, Cunha Neto MB, Czepielewski MA, Duarte FH, Faria MD. Controversial issues in the management of hyperprolactinemia and prolactinomas—An overview by the Neuroendocrinology Department of the Brazilian Society of Endocrinology and Metabolism. *Archives of endocrinology and metabolism*. 2018 Mar;62(2):236-63. <https://doi.org/10.20945/2359-3997000000032>
4. Atluri S, Sarathi V, Goel A, Boppana R, Shivaprasad C. Etiological profile of galactorrhoea. *Indian journal of endocrinology and metabolism*. 2018 Jul;22(4):489. https://doi.org/10.4103/ijem.ijem_89_18

5. Samperi I, Lithgow K, Karavitaki N. Hyperprolactinaemia. *Journal of clinical medicine*. 2019 Dec;8(12):2203. <https://doi.org/10.3390/jcm8122203>
6. Patrascu OM, Chopra D, Dwivedi S. Galactorrhoea: Report of two cases. *Mædica*. 2015 Jun;10(2):136.
7. Chen AX, Burt MG. Hyperprolactinemia. *Australian prescriber*. 2017 Dec;40(6):220.
8. Aziz K, Shahbaz A, Umair M, Sharifzadeh M, Sachmechi I. Hyperprolactinemia with galactorrhea due to subclinical hypothyroidism: a case report and review of the literature. *Cureus*. 2018 May;10(5). <https://doi.org/10.7759/cureus.2723>
9. Shenenberger D. Hyperprolactinaemia: Practice Essentials, Pathophysiology, Epidemiology. *Emedicine.medscape.com*. <https://emedicine.medscape.com/article/121784-overview#a1>
10. John E, Guyton AC. *Guyton and Hall Textbook of Medical Physiology*. Saunders/Elsevier; 2011.
11. Ansari MS, Almalki MH. Primary hypothyroidism with markedly high prolactin. *Frontiers in endocrinology*. 2016 Apr 26;7:35. <https://doi.org/10.3389/fendo.2016.00035>
12. Kanasaki H, Oride A, Mijiddorj T, Kyo S. Role of thyrotropin-releasing hormone in prolactin-producing cell models. *Neuropeptides*. 2015 Dec 1;54:73-7. <https://doi.org/10.1016/j.npep.2015.08.001>
13. Foord SM, Peters JR, Dieguez C, Jasani B, Hall R, Scanlon MF. Hypothyroid pituitary cells in culture: an analysis of thyrotropin and prolactin responses to dopamine (DA) and DA receptor binding. *Endocrinology*. 1984 Jul 1;115(1):407-15. <https://doi.org/10.1210/endo-115-1-407>
14. Bahar A, Akha O, Kashi Z, Vesgari Z. Hyperprolactinemia in association with subclinical hypothyroidism. *Caspian Journal of internal medicine*. 2011;2(2):229.
15. Nallusamy S, Gracelyn LJ. Prevalence of hyperprolactinemia in infertile women and its association with hypothyroidism. *Int J Adv Med*. 2016 Jan;3:33-8. <https://doi.org/10.18203/2349-3933.ijam20151533>
16. Sharma LK, Sharma N, Gadpayle AK, Dutta D. Prevalence and predictors of hyperprolactinemia in subclinical hypothyroidism. *European journal of internal medicine*. 2016 Nov 1;35:106-10. <https://doi.org/10.1016/j.ejim.2016.07.012>
17. Koner S, Chaudhuri A, Biswas A, Adhya D, Ray R. A study on thyroid profile and prolactin level in hypothyroid females of a rural population of a developing country. *Medical Journal of Dr. DY Patil Vidyapeeth*. 2019 May 1;12(3):217. https://doi.org/10.4103/mjdrdypu.mjdrdypu_121_18
18. Valerie West P, Michael W. Feltz M. Hypothyroidism: A Clinical Case Review - Page 2 of 2 - Clinical Advisor. *Clinical Advisor*. 2021. <https://www.clinicaladvisor.com/home/topics/endocrinology-information-center/hypothyroidism-a-clinical-case-review/2/>
19. Majumdar A, Mangal NS. Hyperprolactinemia. *Principles and Practice of Controlled Ovarian Stimulation in ART*. 2015:319-28.
20. Pelosi MA, Langer A, Zanvetto J, Devanesan M. Galactorrhea associated with primary hypothyroidism. Report of two cases. *Obstetrics and gynecology*. 1977 Jan 1;49(1 suppl):12-4.
21. Keye WR, Yuen BH, Knopf RF, Jaffe RB. Amenorrhea, hyperprolactinemia, and pituitary enlargement secondary to primary hypothyroidism. Successful treatment with thyroid replacement. *Obstetrics and gynecology*. 1976 Dec 1;48(6):697-702. <https://doi.org/10.1097/00006254-197705000-00020>
22. Khorassanizadeh R, Sundaresh V, Levine SN. Primary Hypothyroidism with Exceptionally High Prolactin-A Really Big Deal. *World Neurosurg*. 2016 Jul; 91:675. e11-4. doi: 10.1016/j.wneu.2016.04.103. Epub 2016 May 4. PMID: 27155380. <https://doi.org/10.1016/j.wneu.2016.04.103>