Case study

PROLACTIN-SECRETING PITUITARY MACROADENOMA PRESENTING WITH HORMONAL DEFICIENCIES CHARACTERISED BY HYPOPITUITARISM AND NEUROGENIC DIABETES INSIPIDUS: a case report and review.

ABSTRACT

We describe and review a case of a prolactin producing pituitary tumor with hypopituitarism and neurogenic diabetes insipidus in a nulliparous woman of Afro-Caribbean origin. The patient presented with dull-aching headaches associated with worsening vision, nausea, and vomiting. She also complained of polyuria, nocturia, thirst, polydipsia, and weight gain. Physical examination on presentation was positive for bilateral visual field deficits, while investigations revealed hypernatremia and elevated plasma osmolality but decreased urine sodium concentration, osmolality, and specific gravity.

The hormonal profile showed high plasma prolactin levels (127.7ng/ml), a low plasma concentration of antidiuretic hormone (0.7pmol/L), and decreased levels of other anterior pituitary hormones. Imaging revealed a large, uncalcified, cystic pituitary mass in the sella turcica measuring 2.46 x 3.16 x 2.69cm in dimension, extending superiorly into the diaphragmatic sella with compression of the optic chiasm and laterally into the cavernous sinus and compression of the internal carotid artery. The outcome of the water deprivation test and desmopressin administration were consistent with neurogenic diabetes insipidus, and a diagnosis of Prolactin-producing pituitary macroadenoma with hypopituitarism and neurogenic diabetes insipidus was made. The patient was commenced on medical treatment and referred for histopathological diagnosis and possible definitive treatment.

Key Words: Pituitary adenoma, Pituitary macroadenoma, Hypopituitarism, Neurogenic diabetes insipidus.

BACKGROUND

Pituitary adenomas are benign tumors of the cells of the anterior lobe of the pituitary gland. In the general population, pituitary adenomas are the most common type of intracranial tumor after meningiomas, gliomas, and schwannomas and have been found to account for 10-15% of all intracranial tumors. [1] The prevalence of these tumors has been rising over the past decades due to increasing awareness within the medical community, access to hormonal assays, and advances in diagnostic imaging. From different parts of the world, several population-based studies have been carried out to report the prevalence of these tumors. A study from Iceland reported a prevalence rate of 115.57 cases per 100,000 people [2].

A cross-sectional survey by Daly et al. carried out in a province in Liege, Belgium, reported a similar prevalence rate of 94 cases per 100,000 individuals in the population studied [3]. In another study conducted in Banbury (Oxfordshire), UK, by Fernandez et al., they reported a prevalence rate of 77.6 cases per 100,000 individuals in the population studied. Fernandez A. et al. also showed that pituitary adenomas were more common in females (66.7%) than in males (33.3%), although the nonfunctional adenoma (NFA) subtype was more common in males. Their study reported a prevalence rate of 58.7% for microadenomas and 41.3% for macroadenomas [4]. Ezzat et al. conducted a meta-analysis to study the prevalence of these tumors. They reported it to be as high as 14.4% from postmortem samples and 22.5% from imaging studies, with an average of 16.7% in the general population. In comparison, the prevalence rate of pituitary macroadenomas was reported to be 0.16 – 0.20% [5].

Pituitary adenomas are classified based on size, hormonal activity, or immunohistochemistry of the cell type of origin [6]. In 2004, the WHO published a comprehensive classification system for pituitary adenomas based on immunohistochemistry, the presence or absence of secretory products, and various other ultrastructural features [7]. Based on their size, pituitary adenomas are classified as microadenomas, macroadenomas, and giant pituitary adenomas. Pituitary adenomas smaller than 1cm in dimension are described as microadenomas, while those greater than or equal to 1cm in size are described as macroadenomas. Giant pituitary adenomas are greater than 4cm in dimension and tend to be invasive with significant mass effects and destruction of the sella turcica. [2, 8]. Based on hormonal activity, which is most useful clinically, pituitary adenomas are classified into functional and nonfunctional adenomas (NFA) (1).

Functional pituitary adenomas are composed of hormonally active cell type(s) secreting one or more hormones. In contrast, nonfunctional pituitary adenomas (NFA) do not secrete hormones but may compress adjacent structures and lead to hormonal deficiencies [9]. Examples of functional pituitary adenomas include prolactinomas, growth hormone-secreting pituitary adenomas, adrenocorticotrophic hormone-secreting pituitary adenomas (ACTHomas), thyroid-stimulating hormone-producing pituitary adenomas (TSHomas) and gonadotrophic hormone-secreting pituitary adenomas [2, 8, 10, 11, 12].

Slow-growing and nonfunctional microadenomas discovered on radiological and postmortem examinations are described as incidentalomas. In a study conducted in Iceland on 410 patients with pituitary adenomas, 43% were found to be non-functional adenomas, 40% were prolactin-secreting adenomas, 11% were growth hormone (GH) secreting adenomas, and 6% were

adrenocorticotropic hormone (ACTH) secreting adenomas. Functional plurihormonal pituitary adenomas (PHAs) have also been described and account for 10 – 15% of all pituitary adenomas. These may be monomorphous with one cell type or plurimorphous with two or more cell types (13). Using immunohistochemistry staining, pituitary adenomas are classified into pink-staining or acidophilic adenomas, which account for about 45% of all cases, and blue-staining or basophilic adenomas, which are less than 20% of all cases. The pink-staining tumors include prolactinomas and growth hormone-secreting pituitary adenomas, while blue-staining tumors comprise ACTHomas, TSHomas, and gonadotrophic hormone-secreting adenomas. Nonfunctional pituitary adenomas that stain positive for synaptophysin have also been identified and are described as null-cell pituitary adenomas. [2] [14] [27]

Out of all pituitary adenomas, prolactinomas are the most common and account for about 29% of all pituitary adenomas and 43% of acidophilic pituitary adenomas. Classically, clinical presentations in women occur as galactorrhea-amenorrhea and infertility, while decreased libido, impotence, and infertility are commonly seen in men. Recognizing possible clinical manifestations of hormonal imbalances from these tumors helps guide the classification, management, and prognosis of patients. Generally, prolactinomas can be managed medically with dopamine agonists or somatostatin analogs to suppress prolactin synthesis and release. [1]

The treatment of choice is surgical in the form of endoscopic transsphenoidal resection. This surgical option is especially preferred in patients with compressive mass effects who present with neurological deficits or visual defects or in patients who do not respond to medications. The procedure is known to be potentially curative for microadenomas and smaller macroadenomas. Radiotherapy options are also available when the other options are not effective. This report aims to present a rare case of prolactin-producing pituitary macroadenoma associated with hypopituitarism, hormonal deficiencies, and diabetes insipidus secondary to mass effects in a nulliparous woman. [1]

CASE REPORT

A 42-year-old nulliparous woman presented to the clinic with a headache described as a dull-aching pain over the past year. Her complaint was associated with progressively worsening vision, nausea, and vomiting. She also complained of feeling thirsty, polyuria of about 6 – 9 L/day, nocturia, and polydipsia. Over the past two years, she experienced a weight gain of about 10kg and has also experienced a six-month history of amenorrhea, but with no breast discharge, neck swelling, heat, or cold intolerance. There was no history of head injury, hearing loss, tinnitus, nystagmus, or vertigo in her. A review of symptoms revealed poor sleep, muscle weakness, fatigue, and bone pains in her shoulder and pelvic regions. There was no fever, cough, shortness of breath, chest pain, or palpitations. Past history was positive for poorly controlled high blood pressure, seasonal allergies, and a mood disorder. Her medications included Lisinopril 10mg, Nifedipine 30mg, and atorvastatin 25mg daily, to which she has not

been compliant. Family history was not contributory, and she does not use alcohol, nicotine, or other recreational drugs.

Physical examination on presentation showed an anxious but well-oriented middle-age female who was afebrile, not pale with bilateral pedal edema. Vital signs revealed and a body temperature of 98F a pulse rate of 69/min, blood pressure of 153/102mmHg and respiratory rate of 14/min. Her BMI was 36.57kg/cm2. Chest and abdominal examinations findings were normal. Ophthalmologic assessment showed mild refractive error and normal confrontation visual field test in both eyes .Visual field examination revealed visual field deficits bilaterally (Figure 1), and the findings on Ichihara's chat was normal for both eyes.

During her visit, her electrolyte panel revealed serum sodium of 160mmol/L (normal 135 – 145mmol/L), serum potassium of 4.1mmol/L (normal 3.5 – 5.0mmol/L), blood urea nitrogen of 4.6mg/dl (normal 6 – 24mg/dl), serum creatinine of 0.4mg/dl (normal 0.6 – 1.2mg/dl), serum calcium of 8.5mg/dl (normal 8.5 – 10.2mg/dL). Her random blood glucose was 146mg/dl (normal <200mg/dl), with an HbA1c of 6.1% (normal < 6.5%). The lipid profile showed a serum low-density lipoprotein (LDL) of 5.3mmol/L (normal < 3.4mmol/L) and serum cholesterol of 7.0mmol/L (normal < 5.2mmol/L). Her hormonal profile showed an elevated serum prolactin level of 127.7ng/ml (normal <20ng/ml), serum follicle-stimulating hormone of 2.6IU/L (4.5 - 21.5IU/L), serum luteinizing hormone of 3.9IU/L (5 - 25IU/L), serum thyroid stimulating hormone of 0.1mU/L (normal 0.5 – 5.0mU/L), serum free thyroxine of 0.3 ng/dL (normal 0.7 – 1.9ng/dL), serum cortisol of 3.2mcg/dL (normal 5 – 25mcg/dL), and serum antidiuretic hormone level of 0.5pmol/L (normal range 0.9 – 4.6pmol/L).

Urinalysis showed a slightly decreased urinary sodium of 19mEq/L (normal >20mEq/L) and a urine osmolality of 35mosm/Kg (50 – 1400mOsm/kg), and specific gravity of 1.001 (normal 1.005 – 1.030). Plasma osmolality 365mosm/Kg (275 -290 mOsm/kg). In the course of performing the water deprivation test there was no significant change in urine volume or concentration. The parameters, however, improved moderately with desmopressin administration with plasma osmolality measure at 295mOsm/Kg. Her routine beta-hCG test was negative. The MRI scan (Brain) showed a large, uncalcified, cystic pituitary mass in the sella turcica measuring 2.46 x 3.16 x 2.69cm in dimension, extending superiorly into the diaphragmatic sella with compression of the optic chiasm, and laterally into the cavernous sinus with compression 50% of the internal carotid artery. (Figure 2) The Pituitary tumor and the extent of local invasion are better appreciated on the multimedia attachments labelled 1 to 16. (Figure 3)

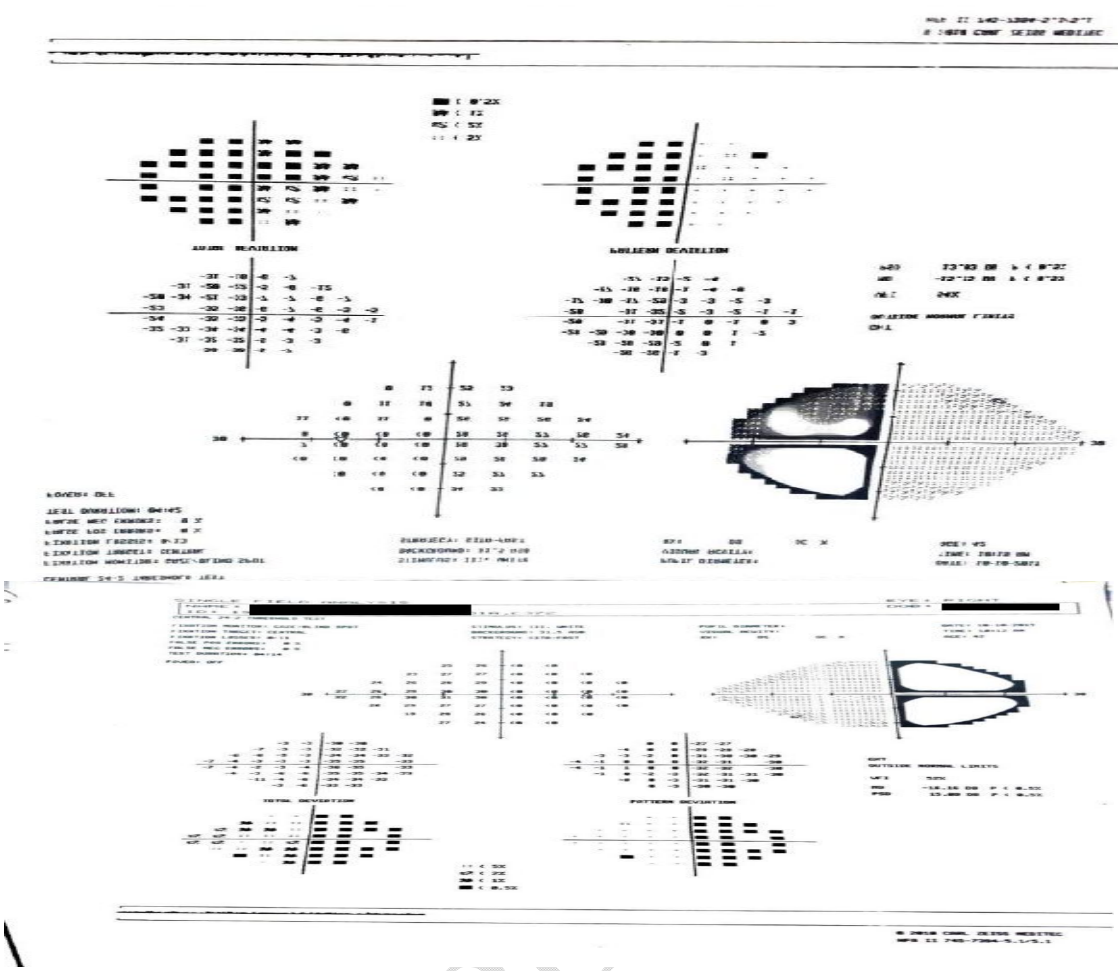

Figure 1: Visual field examinations showing multiple abnormalities bilaterally (homonymous hemianopia and quadrantanopia)

Source: **Caribbean Kidney and Medical Center** (Library).

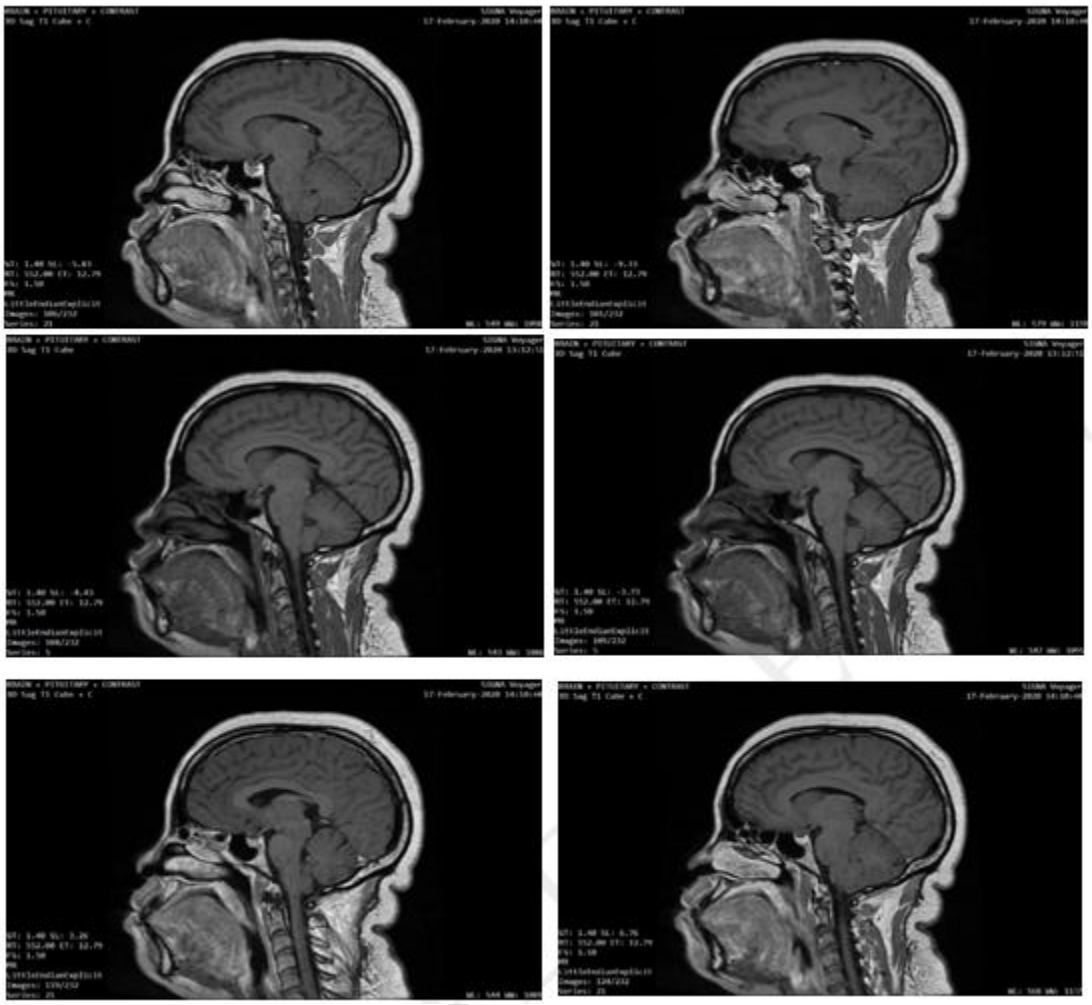

Figure 2: Baseline magnetic resonance imaging (MRI) showing the multilayer sagittal sections of the patient with an uncalcified mass on the sella turcica pushing anteriorly and downward. .

Source: **Caribbean Kidney and Medical Center** (Library).

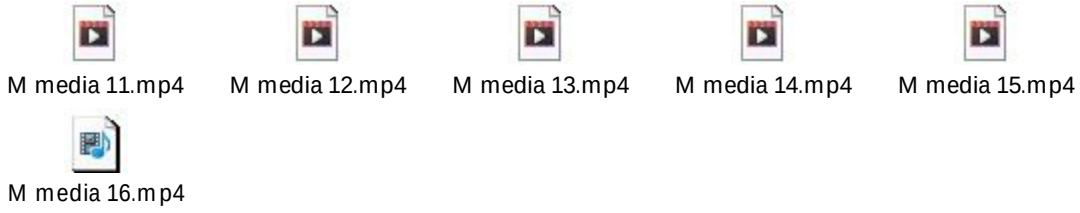

Figure 3: Multimedia (mp) 1 to 16 demonstrated differing visual layers of the pituitary tumor. The MRI scan (Brain) showed a large, uncalcified, cystic pituitary mass in the sella turcica measuring 2.46 x 3.16 x 2.69cm in dimension, extending anterio-superiorly into the diaphragmatic sella with compression of the optic chiasm, and laterally into the cavernous sinus with compression 50% of the internal carotid artery.

Source: **Caribbean Kidney and Medical Center** (Library).

Given the patient's history and physical and investigation findings, an assessment of a prolactin-producing pituitary macroadenoma with hypopituitarism, hormonal deficiencies, and neurogenic diabetes insipidus was made. She was commenced on oral bromocriptine (Parlodel) 2.5mg daily and intranasal desmopressin spray (DDVAP) 20mcg twice daily. She was referred for a neurosurgery consult in Barbados for further evaluation and definitive treatment. As of the time of documentation of this report, the patient was stable and awaiting further evaluation.

DISCUSSION

Pituitary adenomas are unique tumors arising from the cells of the anterior pituitary, usually with characteristic findings. Most pituitary adenomas are slow-growing and benign; however, invasive pituitary adenomas with aggressive behavior have been described in the literature. Pituitary adenomas are monoclonal neoplasms in origin. Several different molecular mechanisms that lead to pituitary adenomas have been identified, although, in most cases, the exact molecular pathogenic mechanisms remains unknown. The factors hypothesized to contribute to the initiation of pituitary neoplasia and proliferation include altered growth factors and cell-cycle regulators resulting from epigenetic changes, abnormal hormonal milieu, abnormal intrapituitary microenvironment, and inherited genetic or somatic mutations; however, most cases are sporadic [14].

The clinical presentations of pituitary adenomas include progressive visual and endocrine manifestations and generally depend on the tumor size and functional status [7, 25]. Typically, slow-growing functional microadenomas and large, fast-growing functional macroadenomas produce hormonal effects. In contrast, all macroadenomas: functional and nonfunctional, can have neurological symptoms like headaches, visual field defects from compression of the optic nerve and optic chiasm, symptoms of hypopituitarism from compression of functional cells, and other mass effects of an intracranial mass. [2] Pituitary microadenomas are usually detected as incidental findings on MRI scans, and patients are typically asymptomatic unless the tumor is

functional. On the other hand, pituitary macroadenomas present with mass effects from compression of adjacent structures and hormonal deficiencies or excess. Sudden hemorrhage or infarction into an existing pituitary adenoma is a presentation that is well recognized and is described as pituitary apoplexy. The condition, however, is uncommon and usually presents as a life-threatening endocrine emergency with sudden and severe headaches, vision loss, and hormonal deficiencies. [15]

In this case report, the clinical presentations may be explained by the mass effects of the macroadenoma. The patient presented with visual field deficits from compression of the optic chiasm leading to visual field deficits in the form of tunnel vision (bitemporal hemianopsia, bitemporal quadrantanopia), confirmed by visual field test and laboratory results showing low thyroid hormones (TSH, T3). Weight gain is most likely a manifestation of secondary hypothyroidism in this patient. [1][16][26][28]

Anatomically, the pituitary gland sits inferior to the hypothalamus. The gland is surrounded caudally by the sphenoid bone and on the cranial aspect by the optic chiasm. It sits in the sella turcica, a basketlike saddle-shaped structure formed as a depression of the sphenoid bone. With tumor growth, the sella turcica thus forces the gland superiorly, leading to compression of the optic chiasm, worsening visual impairment, and headaches secondary to mass effect, as reported in this case. The visual impairment correlates with tumor size and has been reported in approximately 40% to 60% of patients. [1][17] Suprasellar extension of the pituitary adenoma with compression of the optic chiasm leading to visual field deficits is most common.

Bitemporal hemianopsia defects are the most prevalent pattern of visual field deficit, followed by homonymous defects. The lateral extension of the adenoma into the cavernous sinus may compress cranial nerves III, IV, and VI and lead to diplopia, but these are not present in the patient. [18] As reported in this patient, the lateral extension into the cavernous sinus may also occur and compress the internal carotid artery. Headache is common and most likely a feature of a macroadenoma. [19] However, it does not correlate with tumor size but is a non-specific symptom due to the stretch of the dural sheath with tumor growth. [1]

The patient was evaluated as a case of a prolactin-producing pituitary macroadenoma with hypopituitarism presenting with secondary hypothyroidism, secondary hypogonadism, secondary hypocortisolism, and neurogenic diabetes insipidus. The hyperplasia of prolactin-secreting acidophils led to prolactinoma and hyperprolactinemia in the patient. The compressive effects of the macroadenoma on the pituitary stalk may disrupt the transport of dopamine down the portal vessels to the anterior pituitary, removing its inhibitory effect on prolactin synthesis and contributing to the increased release of prolactin. This compressive effect is known as the stalk effect. [19][20][28]

In patients with pituitary macroadenomas, hypopituitarism may result from mass effects, compression, and suppression of functional cells of the anterior pituitary and present with hormonal deficiencies, as observed in this patient.[1][21][22] Hormonal deficiency may also occur in the setting of compression of the pituitary stalk and neurodegeneration in the posterior pituitary. [22]These mechanisms explain the impaired hormonal profile and the low levels of serum TSH, FSH, LH, free T4, cortisol, and ADH seen in the patient. [9][23][24]

A decrease in thyrotropin-releasing hormone (TRH) secretion may occur due to negative feedback exerted by the elevated serum prolactin levels on the thyroid axis. This physiological effect would reduce the synthesis and secretion of thyroid-stimulating hormone from thyrotrophic cells of the anterior pituitary and of thyroid hormones from the thyroid gland. This mechanism may explain the low levels of serum TSH and free T4 in this patient, but another contributing factor would be the mass effect of the macroadenoma on thyrotrophic cells. These mechanisms explain the presentation of secondary hypothyroidism in the patient and may contribute to her fatigue and weight gain. [16][27][28] Additional manifestations of secondary hypothyroidism include cold intolerance, constipation, and bradycardia, among others.

The low serum luteinizing hormone (LH), low follicle-stimulating hormone (FSH), and secondary hypogonadism seen in the patient may be explained by a combination of mechanisms. Elevated serum prolactin is known to exert an inhibitory effect on the synthesis and pulsatile release of gonadotrophin-releasing hormone from the hypothalamus, leading to downregulation of the hypothalamic-pituitary-ovarian axis. [17][18][19][20][21] In addition, the mass effects of the macroadenoma may cause the compression and suppression of gonadotrophic cells and contribute to the secondary hypogonadism seen in this patient. The classical manifestations of hypogonadism in women include inhibition of follicular development and ovulation from decreased FSH and LH, infertility, amenorrhea, and galactorrhea. In men, common clinical findings include reduced libido, erectile dysfunction, and infertility. Gynecomastia, bone pains, osteopenia, and osteoporosis are additional presentations of hypogonadism that may be seen in both sexes. [23]

Additional manifestations of the hypopituitarism seen in the patient include secondary hypocortisolism with a deficiency of ACTH. This would lead to cortisol deficiency and present with fatigue, dizziness, nausea, vomiting, abdominal pain, arthralgia, low-stress intolerance, low blood pressure, and weight loss, some of which were seen in the patient. The deficiency of growth hormone (GH) may also occur and present with fatigue and weight gain. [17][18][19][20]

Neurogenic diabetes insipidus rarely occurs as a coexisting presentation with a pituitary macroadenoma. In literature, it has been widely reported as a complication following endoscopic transsphenoidal resection for a pituitary adenoma, with metastatic disease of the pituitary gland, or following steroid treatment for pituitary apoplexy. [21][22][23] In the absence of these associations, neurogenic diabetes insipidus seen in this patient most likely occurred with the growth of the pituitary macroadenoma, stalk effect, and neurodegeneration of the axons of the magnocellular neurons descending from the supraoptic and paraventricular hypothalamic nuclei to the posterior pituitary. [23][24] This mechanism of neurogenic diabetes insipidus explains its possible coexistence as a clinical manifestation of pituitary

macroadenoma. The presentation is characterized by polyuria, nocturia, dehydration, thirst, and polydipsia in the presence of euglycemia and may be complicated by seizures. Psychiatric manifestations like depression, anxiety, apathy, emotional instability, and irritability may also be observed. [17][23]

The diagnosis of pituitary adenomas is usually made from clinical presentations, investigations, and imaging to rule out possible differentials and confirm the diagnosis. Generally, MRI scans are considered the imaging modality of choice for pituitary pathologies because of their multiplanar capability and their good soft tissue serving as contrast. [11][25][26] Treatment generally includes medical and surgical options. Dopamine agonists, somatostatin analogs, and growth hormone receptor antagonists are routine options for tumor shrinkage. [25] However, surgical decompression can be considered when patients are intolerant of medications or when they become ineffective. The definitive treatment for pituitary adenomas is trans-sphenoidal adenomectomy. [25][26] Radiotherapy and proton therapy are additional options and can be considered when medical and surgical options become ineffective. [25][27] Replacement of hormonal deficiencies may be required for these patients. Prognosis generally depends on the tumor size, functional status of patients, presence of comorbidities, and facilities available. Macroadenoma tends to enlarge more frequently at 12.5 per 100 patient-years (95% CI 7.9-17.2), while microadenoma is lower at 3.3 per 100 patient-years (95% CI 2.1-4.5). [8][28][29]

CONCLUSION

Pituitary adenomas are common benign tumors in the general population. Although the prevalence of these tumors has been rising, a pituitary macroadenoma presenting with hypopituitarism and neurogenic diabetes insipidus, as reported in this case, is uncommon. The association of neurogenic diabetes insipidus with pituitary adenomas which appears as a presentation in this patient, has mostly been documented in literature as a complication following surgical treatment for pituitary adenomas, steroid treatment for pituitary apoplexy, or metastatic disease of the pituitary gland. Thus, it is important to remember and recognize it as a possible presenting symptom in patients with pituitary macroadenomas.

In this case, we believe the presentation of neurogenic diabetes insipidus occurred as an extension of the stalk effect due to the compression of axons descending from hypothalamic nuclei to the posterior pituitary by the macroadenoma. Although surgical evaluation and histopathological assessment were unavailable at the time of writing this report, the clinical

manifestations and investigation findings in this patient were consistent with the rare diagnosis of prolactin-producing macroadenoma with hypopituitarism, hormonal deficiency, and neurogenic diabetes insipidus.

DISCLAIMER

There is absolutely no conflict of interest between the authors, .facilities and the government. The research is solely for academic purposes in the advancement of medical knowledge with sole aim of improving the lives of our patients. Also, there is no financial supports from any source, it is solely funded by the Authors.

CONSENT AND ETHICAL APPROVAL

The Ministry of Health and Wellness, Saint Vincent the Grenadines, approved the research works.
Consent form signed by the patient, witness, and physicians.

REFERENCES

1. Lake MG, Krook LS, Cruz SV. Pituitary adenomas: an overview. *Am Fam Physician.* 2013; 88(5):319-327.
2. James, K. S., Franklin, A. M., & Brian, F. M. (Eds.). (2009). *The Cleveland Clinic Intensive Review of Internal Medicine* (Fifth Edition ed.). Cleveland: Lippincott Williams & Wilkins.
3. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. *J Clin Endocrinol Metab.* 2006; 91(12):4769-4775. DOI: 10.1210/jc.2006-1668.
4. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin Endocrinol (Oxf).* 2010; 72(3):377-382. doi: 10.1111/j.1365-2265.2009.03667.
5. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, McCutcheon IE. The prevalence of pituitary adenomas: a systematic review. *Cancer*. 2004; 101(3):613-619. DOI: 10.1002/cncr.20412.
6. Bidari-Zerehpoosh F, Sharifi G, Novin K, Mortazavi N. Invasive growth hormone-producing pituitary adenoma with lymphocytic infiltration: a case report and literature review. *Iran J Cancer Prev.* 2015; 8(6): e3504. DOI: 10.17795/JCP-3504.
7. Chatzellis E, Alexandraki KI, Androulakis II, Kaltsas G. Aggressive pituitary tumors. *Neuroendocrinology.* 2015; 101(2):87-104. DOI: 10.1159/000371806.
8. James, R. M., & Dimitry, A. P. (2018, September 04). *Pituitary Macroadenoma*. (T. Francisco, S. Yoram, & T. G. George, Editors) Retrieved from Medscape:
9. Russ S, Shafiq I. Pituitary Adenoma. 2020. Stat Pearls Publishing, Florida, US.
10. S. M., & M. S. (1980). Functional classification of pituitary adenomas. *Acta Neurochirurgica*, 52 (3–4): 195–202. doi:10.1007/bf01402074
11. Shereen, E., Sylvia, L. A., William, T. C., Charles, E. B., William, E. D., Mary, L. V., & Ian, E. M. (2004). The prevalence of pituitary adenomas. *American Cancer Society*.

12. Li, J., et al., *Case report of a pituitary thyrotropin-secreting macroadenoma with Hashimoto thyroiditis and infertility.* Medicine (Baltimore), 2018. **97**(1): p. e9546.
13. Allehaibi, E., M.H. AlMalki, and I. Brema, *Plurihormonal pituitary macroadenoma: a case report.* J Med Case Rep, 2021. **15**(1): p. 407.
14. Caimari F, Korbonits M. Novel genetic causes of pituitary adenomas. *Clin Cancer Res.* 2016; 22(20):5030-5042. doi: 10.1158/1078-0432.CCR-16-0452.
15. Vandeva S, Jaffrain-Rea ML, Daly AF, Tichomirowa M, Zacharieva S, Beckers A. The genetics of pituitary adenomas. *Best Pract Res Clin Endocrinol Metab.* 2010; 24(3):461-476. DOI: 10.1016/j.beem.
16. A-Chalabi, Alsalmann I. Physiology, Prolactin. [Updated 2020 Mar25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing;2020 Jan-
17. Weitzner, M. A., Kanfer, S., & Booth-Jones, M. (2005). Apathy and pituitary disease: it has nothing to do with depression. *The Journal of Neuropsychiatry and Clinical Neurosciences.*, 17 (2): 159–66. doi:10.1176/jnp.17.2.159
18. Nabarro, J. D. (1987, April). Acromegaly. *Clinical Endocrinology. 26 (4)*, 481–512. doi:10.1111/j.1365-2265.1987.tb00805.x
19. Nieman, L. K., & Ilias, I. (2005, December). Evaluation and Treatment of Cushing's Syndrome. *The American Journal of Medicine. 118 (12)*, 1340–6. doi:10.1016/j.amjmed.2005.01.059
20. Kirk Jr, L. F., Hash, R. B., Katner, H. P., & Jones, T. (2000, September 1). Cushing's Disease: Clinical Manifestations and Diagnostic Evaluation. *American Family Physician.*, 62 (5), 1119-27, 1133-4. Retrieved from
21. Biousse, V., Oyesiku, N. M., & Newman, N. J. (2001). Precipitating Factors in Pituitary Apoplexy. *Journal of Neurology, Neurosurgery, and Psychiatry. 71 (4): 542–5*. doi:10.1136/jnnp.71.4.542
22. Machine, M. (2003). Diabetes Insipidus. *Hormone Research. 59 Suppl 1: 42–54*. doi:10.1159/000067844
23. Chapman, I. M. (2019, August). *Acromegaly and Gigantism*. Retrieved from Merck.com:
24. Thomas, A. W. (2015). *Central Diabetes Insipidus*. Retrieved May 28, 2017, from Rare Diseases:
25. Russ S, Shafiq I. Pituitary Adenoma. 2020. Stat Pearls Publishing, Florida, US.
26. Vandeva S, Jaffrain-Rea ML, Daly AF, Tichomirowa M, Zacharieva S, Beckers A. The genetics of pituitary adenomas. *Best Pract Res Clin Endocrinol Metab.* 2010; 24(3):461-476. DOI: 10.1016/j.beem.
27. Newey, P. J., & Thakker, R. V. (2011). Role of Multiple Endocrine Neoplasia Type 1 Mutational Analysis in Clinical Practice. *Endocrine Practice. 17 Suppl 3: 8–17.* doi:10.4158/EP10379.RA
28. Marini, F. F., A, L. E., Tonelli, F., & Maria, L. B. (2009, July 18). Multiple Endocrine Neoplasia Type 1 (MEN1) Syndrome. (D. Riegert-Johnson, B. LA, T. Hefferton, & M. Roberts, Eds.) *Cancer Syndromes [Internet]. Bethesda (MD): National Center for Biotechnology Information PMID: 21249756*. Retrieved from
29. Daly, A. F., Vanbellinghen, J.-F., & Beckers, A. (2007, November). Characteristics of Familial Isolated Pituitary Adenomas. *Expert Review of Endocrinology & Metabolism. 2 (6): 725–733*. doi:10.1586/17446651.2.6.725