JPSIM Journal of Pakistan Society of Internal Medicine

Case Report

A Study on a 21years Female Patient with Resected Pituitary Macroadenoma Presented with Persistently Raised Growth Hormone Levels and Resistant Diabetes Mellitus

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Abstract

Pituitary neuroendocrine tumors affect round about 5% of the general population. Pituitary macroadenomas have a size greater than 10mm, while microadenoma has a size less than 10mm.4 Acromegaly is a rare but fatal disorder mainly due to excessive growth hormone (GH) production from pituitary adenoma and a secondary rise in IGF-1 levels. It is characterized by physical disfigurement mainly face and limbs. The prevalence of acromegaly is 40 to 70 cases per million inhabitants with an annual incidence rate of 3 to 4 per million.5 The treatment options consist of pituitary surgery with the best approach of endonasal transsphenoidal hypophysectomy. The drugs used for prolactinoma and somatotrophic adenoma are dopamine agonists and somatostatin analogues respectively.

How to cite this:

Banaras F, Fayyaz R, Ashfaq M, Fayaz K, Tahir T, Raza A. A Study on a 21years Female Patient with Resected Pituitary Macroadenoma Presented with Persistently Raised Growth Hormone Levels and Resistant Diabetes Mellitus. J Pak Soc Intern Med. 2023;4(1): 60-62

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Introduction

Pituitary adenomas are generally nonmalignant epithelial tumors originating from adenohypophyseal cells. They are mostly sessile, extensive tumors, limited to sella turcica. Pituitary adenomas can be detected in all groups of ages, however, they are seldom present in adulthood.[1] Pituitary gland adenomas contribute around 15% of all neurological malignancies.[2] They can easily be distinguished from each other by the presence or lack of the hormone, size of tumors, and clinicopathological manifestations. According to World Health Organization (WHO), 85% of pituitary tumors are typical adenomas, while the rest are atypical, showing invasive growth.[3]

Pituitary neuroendocrine malignancies exert influences on about 5% of the general population. The most prevalent pituitary adenomas are prolactinoma secreting prolactin leads to galactorrhea amenorrhea syndrome. The other pituitary adenomas in descending order of occurrence are gonadotrophic, somatotrophic, corticotrophic, and occasionally thyrotrophic, producing gonadotropins(FSH and LH), somatotrophic hormone/ growth hormone (acromegaly), adrenocorticotrophic hormone (Cushing's disease), and thyroid stimulating hormone (central hyperthyroidism), respectively.[4]

Acromegaly is an unusual but fatal disorder mainly due to growth hormone (GH)-producing pituitary adenoma and secondary rise in IGF-1 levels. It is characterized by physical deformation mainly in the face and limbs. The prevalence of acromegaly is 40 to 70 cases per million inhabitants with an annual incidence rate of 3 to 4 per million.[5]

The treatment options comprise pituitary surgery with the best approach of endonasal transsphenoidal hypophysectomy. The medication used for prolactinoma and somatotrophic adenoma are dopamine agonists and somatostatin analogues respectively, however chemotherapy and radiotherapy have been also introduced.

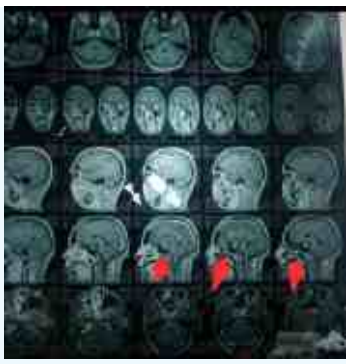
Case Report

A 21 years old female patient known case of diabetes mellitus for 4 years, presented to the outpatient department (OPD), with chief complaints of primary amenorrhea, headache since childhood, blurring of vision, weight loss, and polyuria for 4 years. The patient can't remember when she was exactly well. From childhood she has had headaches, insidious onset, progressively increased for last 4 years mainly in frontal site, radiating to neck region not relieved by NSAIDs. She has primary amenorrhea, no effect despite the use of pills prescribed by local physicians/obstetricians. She has decreased vision with flashes and floaters for the last 4 years. Associated symp-

toms presented are polyuria (increased frequency), weight loss, abdominal distension, and fever on and off. The parents took her to a Hakeem and later to a Pir. They treated her for 'Tabkheer-e-Maida' & 'jins' respectively, but with no relief. The patient is diabetic for 4 years, diagnosed at the age of 17 years, on Mixtard insulin 70/30 (30 units morning, 20 units at night). However no history of diabetes mellitus in the family. She has undergone bilateral cataract surgery. On general physical examination, a young lady was well dressed, built well oriented to time, place, and person but slightly restless and disinterested looking, sitting on the bed. Her B.P is 100/70 mm Hg, Pulse 90/min, SPo2 98%, Temp Afebrile, R/R 18/min, and weight 55kg.

There is no jaundiced, pallor, clubbing, koilonychia, leuconychia edema, thyromegaly, or lymphadenopathy.

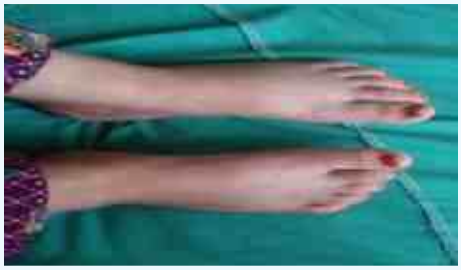
(A) Spade like fingers in acromegaly



(B) Pituitary adenoma MRI

(C) MRI before surgery (adenoma)

(D) MRI after surgery (Recurrance)



Enlarged feet

Table 1: *Laboratory investigations before surgery:*

Hemoglobin	**13g/dl (normal)**	**HbA1C**	**15% (N<6.5%)**
WBC Count	8×10^3 (normal)	Urinalysis	Glucose +3
Platelets	325×10^3 (normal)	Thyroid function tests	Normal
Renal Function tests Liver function tests Serum electrolytes	Normal	Prolactin	12.58ng/ml Normal Range 5.2-27
Parathyroid hormone (PTH) level	64.2ng/dl Normal Range 15-68	Serum cortisol	64.2ng/ml Normal Range15-68
Random blood sugar	**630mg/dl** (RBS<200 mg/dl)	Serum calcium	8mg/dl Normal Range 8-10.5
Growth hormone	**38.5ng/mL** Normal upto 9.9	**Insulin like growth factor (IGF-1)**	**620ng/mL** Normal Range109-399

Still increased increased level of Growth hormone and insulin like growth factor IGF-1 after surgery:

Growth hormone	**11 ng/mL**	**Normal range 2-5**
IGF-1	653ng/mL	Normal range 230-550

The patient has coarse facial features, a slanted forehead, and nose enlargement with supraorbital ridges. She is quite tall(giant), has nose enlargement, spade-like fingers with sweaty skin, having difficulty wearing shoes. Secondary sexual characters, breast development is still in tanner stage II. She has scanty hair growth and a deep voice. There is No prognathism no interdental spaces or organomegaly. PHQ-9 (Patient Health Questionnaire-9) contains nine questions in which each score is from 0 to 3 Total scores are 0 to 27, Her score was 2 suggesting no depression. Ultrasound abdomen and pelvis show small-sized hypoplastic uterus with bilateral hypoplastic ovaries. MRI Brain with contrast shows a lobulated signal mass in the sellar and suprasellar region. The Sellar region mass dimension 2.2×1.8 ×1.5cm while Suprasellar region mass dimension 1× 1.5 × 0.9cm. Open surgery was done and a sample was sent for biopsy which shows pituitary macroadenoma. The post-surgery complications patient developed is diabetes inspidus (started on desmopressin), hypothyroidism (started on thyroxine), and blurring of vision

most likely due to compression of optic chiasma leading to bitemporal hemianopsia. moreover, estrogenization was done for the infantile uterus. The patient growth factor levels, IGF-1 levels, and blood sugar levels are still elevated after open brain surgery suggesting the regrowth of pituitary tumor or tumor is not fully resected.

Discussion

Pituitary adenomas are benign tumors consisting of adenohypophysial cells, primarily arise from sella turcica, and are rarely ectopic. They show the broad spectrum of biological behavior in terms of hormonal and proliferative activities. Pituitary adenomas are rare in teens. About 3.5–8.5% of pituitary adenomas are diagnosed before the second decade. Childhood tumors are more common in females, usually smaller in size, show less invasion, and are less violent as compared to adult tumors.[6]

The most widely used classification of pituitary adenomas proposed by Hardy in 1970 based on radiological investigations shows four grades. Grade I adenomas are microadenomas having a size of less than 1cm, without causing any bony destruction. Grade II adenomas are macroadenomas having a size greater than 2cm, and exhibit suprasellar extension without any invasion or bony erosion. grade III adenomas are large locally invasive tumors that show sellar enlargement and bony destruction. Grade IV adenomas are invasive tumors that involve the surrounding structures like basal ganglia and cavernous sinuses.[7]

Acromegaly is a multisystem disorder primarily due to uncontrolled production of growth hormone and secondary rise in IGF-1 levels. Pituitary somatotrophinoma contributes to more than 95% etiology of acromegaly. Rare causes of acromegaly are ectopic sources like sphenoidal sinus, nasopharyngeal cavity, or clivus. The clinicopathological manifestations of acromegaly are excessive growth of the musculoskeletal system characterized by nose enlargement, prominent supraorbital ridges, slanted forehead, prognathism, maxillary widening, increased interdental spaces, jaw malocclusion, kyphoscoliosis, spade-like finger, deepening of the voice, macroglossia and visceromegaly.[8]

The common complications of acromegaly are concentric biventricular hypertrophy, heart failure, respiratory failure, sleep apnea, morning sleepiness, and migraine. The metabolic complication includes impaired glucose tolerance due to growth hormone-induced insulin resistance and abnormal lipid metabolism. In the fifth decade of life, there is a high risk of colon tumors in acromegalic patients. Acromegalic arthropathy primarily affects knee joints followed by shoulder, hip, ankle, elbow, and phalangeal joints. Endocrine complications include hypogonadism and galactorrhea amenorrhea syndrome.[9]
The primary intention of management in acromegalic patients is to decrease growth hormone to less than 2.5ug/l. Treatment options available are medical therapy, surgery, radiotherapy, and chemotherapy. The medication used for prolactinoma is dopamine agonist (cabergoline), for somatotrophic adenoma, somatostatin analogues(octreotide) and pegvisomant (GH receptor antagonist) are used, followed by transsphenoidal hypophysectomy through nasal approach (Endonasal transsphenoidal hypophysectomy).[10]
The primary aim of surgical therapy in acromegalic patients is to normalize the pulsatile pattern of growth hormone secretion along with IGF-I levels to rid the patient of signs and symptoms of the disease and prevent a recurrence. During early series postoperative patients, the criteria of remission were GH levels less than 5ug/l. In 1998 a study conducted by Ross and Wilson analyzed the results of 30 published series and conclude cure rate was 56% in 153 cases.[11] Another Multicentre study conducted by Zervas, Losa, et al gave a cure rate of 66% in 1256 patients.[12], and Valdemarsson et al.
Postoperative pituitary complications, mainly panhypopituitarism deadly effects the quality of life of patients. The rate of tumor recurrence is strongly related to remission criteria i.e. GH<5ug/l.Considering this remission criterion, a study conducted with a follow-up period of 6 years suggested a recurrence rate of 7% in 61 patients[13] which is similar to studies conducted by Losa et al. and Arafah et al.[14]
In our case study the patient growth factor levels, IGF-1 levels, and blood sugar levels are still elevated after open brain surgery suggesting the regrowth of pituitary tumor or tumor is not fully resected.

Conflict of Interest: *None*

Funding source: *None*

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