CASE REPORT

Lady Surrounded by Multiple Endocrine Neoplasia (MEN)

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Received on: 10 March 2023; *Accepted on:* 20 April 2023; *Published on:* 12 May 2023

Abstract

Secondary adrenal insufficiency (SAI) had been diagnosed in a nondiabetic lady with recurrent hypoglycemia having low morning cortisol and low-normal adrenocorticotropic hormone. Her symptoms persisted despite being on supplemental hydrocortisone. Appropriate workup subsequently documented endogenous hyperinsulinemia. Solitary pancreatic endocrine tumor, primary hyperparathyroidism due to multiglandular pathology, and the presence of multiple collagenomas established the diagnosis of multiple endocrine neoplasia type 1 (MEN1) syndrome. Basal morning cortisol (1.9 µg/dL) was grossly suppressed in this lady, and so was the cortisol value (2.2 µg/dL) measured during hypoglycemia (plasma glucose: 24 mg/dL). Recurrent hypoglycemia due to any cause, results in a functional abnormality of the hypothalamus–pituitary–adrenal (HPA) axis in individuals without primary disease of the HPA pathway. The defect may be severe enough to lower the basal and stimulated cortisol values much below the established cut-offs for adrenal insufficiency, and patients may be misdiagnosed to have adrenal failure. Complete normalization of cortisol values are observed following strict avoidance of hypoglycemia.

Keywords: Adrenocorticotropic hormone, Hypoglycemia, Insulinoma, Multiple endocrine neoplasia.

Bengal Physician Journal (2023): 10.5005/jp-journals-10070-7098

Background

Hypoglycemia, though frequently encountered in patients with diabetes, is somewhat rare in persons who do not have drug-treated diabetes mellitus. The possible etiologies of hypoglycemia in individuals not having diabetes are sepsis, organ failures, counterregulatory hormone (glucagon, epinephrine, cortisol, and growth hormone) deficiency, drugs, endogenous hyperinsulinism, and non-islet cell tumors secreting big insulin-like growth factor 2 (IGF2). Accidental or surreptitious ingestion of insulin secretagogues, insulinoma, insulin autoimmune hypoglycemia, and functional β-cell disorders (nesidioblastosis) give rise to endogenous hyperinsulinism.[1] As a normal defense mechanism, insulin secretion and action are suppressed virtually completely at a mean plasma glucose concentration of approximately 55 mg/dL. Serum insulin, C-peptide, and ketone (β-hydroxybutyric acid) in such "critical sample" are able to distinguish hypoglycemia caused by endogenous (or exogenous) insulin excess from other etiologies. Insulin tolerance test (ITT) is the gold standard test for evaluating the integrity of hypothalamus–pituitary–adrenal (HPA) axis, and a cut-off peak cortisol response of >18 µg/dL during hypoglycemia is taken as a normal response.[2] Endogenous cortisol secretion starts rising when blood glucose falls below 65–70 mg/dL. Counterregulatory hormonal upsurges are relatively preserved in endogenous hyperinsulinism; however, the glycemic thresholds for such responses (and behavioral responses) to falling glucose shift to lower plasma glucose concentrations in patients with recurrent hypoglycemia. With ongoing recurrent and severe hypoglycemia, a functional defect in the intact HPA axis sets in. Both basal morning and "critical sample" cortisol values may be grossly low in such patients leading to an erroneous diagnosis of adrenal insufficiency. Low cortisol following recurrent hypoglycemia in untreated patients of hyperinsulinemic hypoglycemia gets completely reversed after avoidance of hypoglycemia either by surgical removal of insulinoma or by diazoxide treatment in noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) suggesting transient impairment of HPA axis.[3,4]

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How to cite this article: Chakraborty PP, Saha S, Das S, *et al*. Lady Surrounded by Multiple Endocrine Neoplasia (MEN). Bengal Physician Journal 2023;10(1):13–17.

Source of support: Nil

Conflict of interest: None

Patient consent statement: The author(s) have obtained written informed consent from the patient for publication of the case report details and related images.

Case Description

A 47-year-old nondiabetic, normotensive lady had presented to her primary care physician with generalized fatigue and recurrent episodes of behavioral abnormalities for the preceding 2 years. With a working diagnosis of secondary adrenal insufficiency (SAI) due to surreptitious glucocorticoid (GC) ingestion, the lady was put on a replacement dose of hydrocortisone (10 mg/m^2/day). However, her symptoms persisted and she was referred to us for further evaluation. Family members noticed that these episodes were associated with irritability, agitation, slurred speech, and drowsiness without loss of consciousness. Most of these episodes had occurred during late night and early morning hours and were rapidly relieved with oral carbohydrates. The lady repeatedly denied intake of any indigenous medicine, over-the-counter medication, or long-term GC use in any form. None of her family members was on antidiabetic agents. She, however, had been diagnosed with gestational diabetes mellitus

(GDM) during her last pregnancy 20 years back and underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy for uterine leiomyoma 2 years prior to her presentation with us.

Clinical examination revealed an obese lady (body mass index: 34.9 kg/m^2) in low mood with dorsocervical pad of fat without other signs of hypercortisolemia. Her sitting blood pressure was 110/72 mm of Hg. Acanthosis nigricans and skin tags were noted over the nape of the neck along with multiple whitish maculopapular lesions over the trunk suggesting collagenomas (Fig. 1). She developed recurrent episodes of documented hypoglycemia post admission. Whipple's triad was established in each of those episodes. Her family history was noncontributory.

Baseline investigations including complete blood count, liver and renal function tests, serum sodium, and potassium were within normal limits. The rest of the investigations have been summarized in Table 1. Magnetic resonance imaging (MRI) abdomen revealed a 4.1 cm × 3.1 cm × 2.2 cm lesion (hypointense in T1, iso to hyperintense in T2, and hyperintense on STIR sequence) having

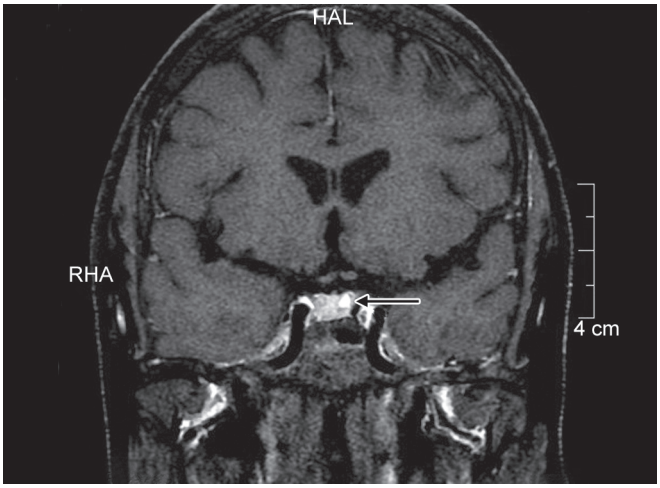


Fig. 1: Contrast enhanced MRI Pituitary (T1, coronal, fat suppressed) showing a microadenoma in left half of Pituitary

Table 1: Summary of investigations

	Patient's value	*Age and sex-specific reference range*
During her presentation with primary care physician		
8:00 am cortisol	1.9	5–25 µg/dL
8:00 am adrenocorticotropic hormone (ACTH) (iced sample)	17.3	10–60 pg/mL
Free thyroxine (FT4)	1.7	0.8–1.8 ng/dL
Total triiodothyronine (TT3)	101	70–200 ng/dL
Thyroid-stimulating hormone (TSH)	3.1	0.5–5 µIU/mL
Magnetic resonance imaging (MRI) scan of pituitary	Microadenoma over the left half of the pituitary with a maximum diameter of 5 mm (Fig. 4)	
Hormonal evaluation post admission from critical sample (plasma glucose <55 mg/dL)		
Plasma glucose	24 mg/dL	
C-peptide	9.28	≥0.6 ng/mL suggests endogenous hyperinsulinism
Insulin	67.5	≥3.0 µIU/mL suggests hyperinsulinism
β-hydroxybutyrate	0.4	≤2.7 mmol/l suggests hyperinsulinism
Cortisol	2.2	>18 µg/dL suggests adrenal sufficiency
Biochemical evaluation post admission		
Albumin-corrected calcium	12.3	8.2–10.2 mg/dL
Phosphorus	2.3	2.5–4.7 mg/dL
Intact parathyroid hormone (iPTH)	530	10–65 pg/mL
25-Hydroxy-vitamin D	28	30–60 ng/mL
Prolactin	12.5	4–30 ng/mL
Fasting gastrin	32	<100 pg/mL
Insulin-like growth factor 1 (IGF1)	119	68–205 ng/mL
Follicle-stimulating hormone (FSH)	98	>30 mIU/mL
Cortisol (1 hour after 250 mcg of intravenous Synacthen)	21.1	>18 µg/dL is considered normal
Laboratory parameters 6 months post surgery		
8:00 AM cortisol	12.4	5–25 µg/dL
Albumin-corrected calcium	8.8	8.2–10.2 mg/dL
Intact parathyroid hormone (iPTH)	51	10–65 pg/mL

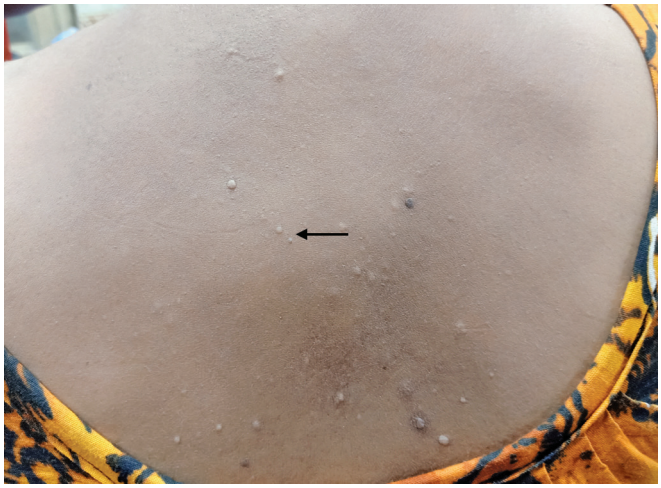


Fig. 2: Multiple maculopapular lesions over back (collagenomas)

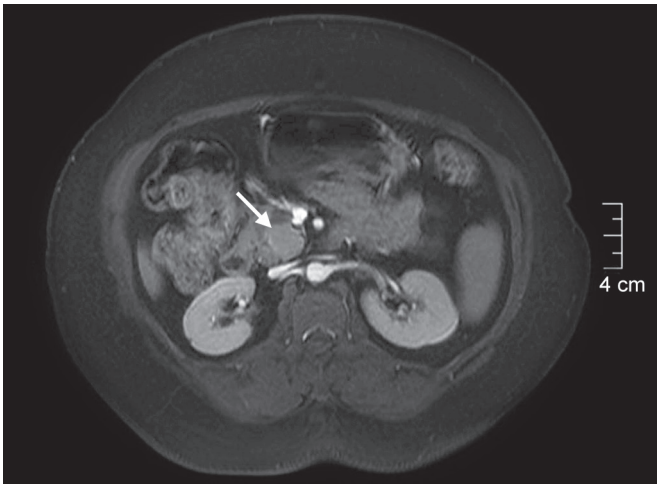
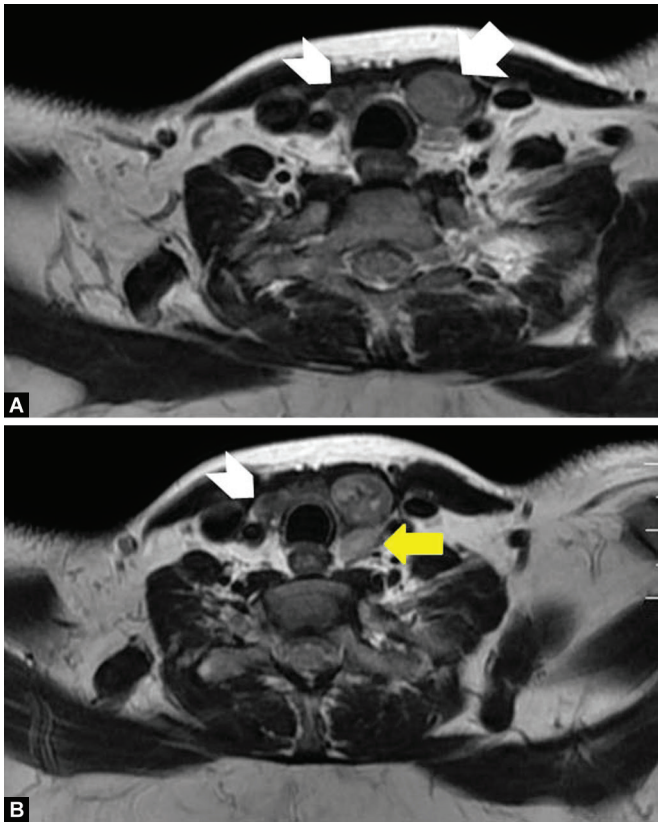


Fig. 3: Solitary enhancing SOL in head and uncinate process of the pancreas (white arrow) on post-contrast T1-weighted MRI



Figs 4A and B: MRI neck showing enlarged left superior (white arrow, upper panel), left inferior (yellow arrow, lower panel), and right superior (white arrowheads) parathyroid glands

lobulated outlines with intense contrast enhancement in the head and uncinate process of the pancreas (Fig. 2).

Magnetic resonance imaging neck documented the following (Fig. 3): 1.7 cm × 1.4 cm mildly heterogeneous partially exophytic space occupying lesion (SOL) (hypointense in T1, hyperintense in T2 and STIR) with contrast enhancement in the posterolateral aspect of the left lobe of the thyroid. Another SOL (2.2 cm × 1 cm) was present at the inferior pole of the left lobe of the thyroid gland (hypointense in T1 and hyperintense in T2 and STIR). The right superior parathyroid gland was also visible (1 cm × 0.5 cm). Ultrasonography-guided needle-tip wash parathyroid hormone (PTH) values from both the SOLs were >2000 pg/mL.

Excision of the solitary pancreatic SOL was carried out along with the removal of the left superior, left inferior, and right superior parathyroid glands. The right inferior parathyroid gland appeared normal in size and morphology; half of that gland was also removed. Surgery was carried out under intravenous hydrocortisone coverage. No further episodes of hypoglycemia occurred after the removal of pancreatic insulinoma. Her mood and generalized fatigability gradually improved. Replacement hydrocortisone was continued post surgery and stopped once the HPA axis recovered completely after 6 months. She was advised for regular follow-up. Family members had been counseled for screening for multiple endocrine neoplasia type 1 (MEN1).

Discussion

The initial diagnosis of SAI was based on low cortisol (1.9 µg/dL) and inappropriately normal adrenocorticotropic hormone (ACTH) (17.3 pg/mL). The usual causes of SAI in this middle-aged lady are exogenous GC use and hypopituitarism. A pituitary microadenoma of less than 6 mm is unlikely to cause hypopituitarism and hormonal evaluations also ruled out this possibility with confidence.[5] Spontaneous recovery of adrenal function 6 months post surgery was also consistent with our diagnosis. Surreptitious or inadvertent GC uses are quite frequent in this part of the world. Hence, she was advised GC supplementation, but, without any effect suggesting a different etiology of hypoglycemia.

About 10% of insulinomas are associated with MEN1 syndrome.[6] Hypercalcemia, hypophosphatemia, and raised serum PTH level were suggestive of primary hyperparathyroidism. Consistent with MEN1 syndrome, this lady also had multiglandular involvement of the parathyroids. Although the most common pituitary tumor in MEN1 is prolactinoma, less than 5% of these tumors are nonfunctioning.[7] This lady may be harboring a nonfunctioning pituitary microadenoma as a component of MEN1 syndrome. However, we could not rule out the possibility of this pituitary microadenoma being an incidentaloma, which has a prevalence of about 10% in the general population.[5] Presence of multiple collagenomas (a prevalence of 70% in this

setting) was an important clue to suspect MEN1-related insulinoma in this patient.[7] Uterine leiomyoma for which she underwent hysterectomy might either be a component of the vast spectrum of this rare syndrome or just a coexisting unrelated finding.[8]

The most intriguing finding, we came across, was grossly diminished basal and "critical sample" cortisol values. Antecedent hypoglycemia reduces counterregulatory responses to subsequent hypoglycemia in healthy subjects and in patients with diabetes. Similar defect is also encountered in untreated patients with hyperinsulinemic hypoglycemia of various etiologies. The plasma glucose thresholds for initiation of both counter-regulation and hypoglycemic symptoms shift to the left, and the magnitude of hormonal response is also blunted.[9] The expected incremental responses of glucagon, epinephrine, and cortisol are uniformly impaired across different studies; however, the predicted rise of growth hormone during hypoglycemia may or may not be observed.[4,10] "Critical sample" cortisol concentrations in these patients are often less than 18 µg/dL, the cut-off value for the gold standard ITT for detection of abnormal HPA axis. In one of the studies involving 84 children with fasting hypoglycemia, the specificity of a low cortisol level (<18 µg/dL) for adrenal insufficiency was 40%.[10]

The reduced cortisol response to recurrent hypoglycemia is not due to primary adrenal insufficiency, and adrenal function testing by exogenous ACTH administration is not impaired by immediate prior exposure to hypoglycemia.[11] This finding was also encountered in this lady. This discrepancy between post-ITT and post-Synacthen cortisol values might play a role to differentiate "true" hypocortisolism from functional hypocortisolism of recurrent hypoglycemia. However, it needs to be remembered that the sensitivity of short Synacthen test to diagnose SAI is relatively low, and many patients of "true" secondary hypocortisolism are able to mount an adequate cortisol response following 250 µg of Synacthen, particularly if the duration of SAI is not long. The defect probably lies in the hypothalamus as cortisol responses following both the ACTH stimulation test (short Synacthen test) and corticotropin-releasing hormone (CRH) are found to be normal.[4] However, desmopressin (1-deamino-8D-arginine vasopressin, DDAVP) fails to mount an adequate incremental response of ACTH and cortisol.[3] Adrenocorticotropic hormone secretion by AVP, synthesized in the parvocellular neurons of the paraventricular neurons is mediated by V1A (V3) receptors. The lack of response to desmopressin in this particular study can be explained by more selectivity of desmopressin toward V2 receptor over the V1A (V3) receptor compared to native L-arginine vasopressin.

The degree of diminished cortisol response in this lady was striking. In one of the earlier reports even after 6 months of avoidance of hypoglycemia, AM cortisol was 2.28 µg/dL and one of the cortisol values during ITT was 4.3 µg/dL (simultaneous glucose: 13 mg/dL) that normalized only after 12 months of successful treatment.[4]

Corticotropin-releasing hormone motor neurons originate from the paraventricular nucleus of the hypothalamus (PVH). The key glucosensing elements for CRH release, however, are located in the hindbrain rather than the hypothalamus. When stimulated by low glucose (<55 mg/dL), these sensors engage catecholaminergic projections that densely innervate the PVH. Following recurrent hypoglycemia, a state of "energy deprivation" sets in. These glucose-sensing neuronal cells then respond to it by increasing noninsulin-mediated glucose transport across cells (by mobilizing glucose transporter 1 from the cytosolic pool to the cell membrane) or by efficient metabolism of the available glucose. In addition, they increase their ability to use alternate fuels and develop tolerance to hypoglycemia.[12] Markedly reduced serum cortisol (0.59 µg/dL) has also been documented during hypoglycemic episodes (plasma glucose 24 mg/dL) in a lady with recurrent hypoglycemia secondary to primary hypothyroidism and morning cortisol normalized once hypoglycaemic episodes were averted with levothyroxine.[13] This suggests that the functional defect of HPA axis is secondary to hypoglycemia only, and hyperinsulinemia, per se, does not play a role. Complete recovery of HPA axis occurs once hypoglycemia is avoided. It may take 6 weeks, 6 months, or even a year.[3,4,13]

Conclusion

Take-home Message

- A diagnosis of MEN1 may be established by the presence of two or more primary MEN1-associated endocrine tumors (parathyroid adenoma, enteropancreatic tumor, and pituitary adenoma). Possibility of MEN1 should always be excluded in patients with insulinoma and a careful general survey for collagenomas or angiofibromas may give us a clue to underlying MEN1.
- Long-standing adrenal insufficiency (either primary or secondary) may be associated with fasting hypoglycemia in adults. Insulin and C-peptide values, when measured during hypoglycemia, are appropriately suppressed in such cases.
- Recurrent episodes of low blood glucose in patients with hyperinsulinemic hypoglycemia give rise to functional abnormalities of HPA axis. It includes left-ward shift of glycemic threshold for incremental cortisol response, blunting of peak cortisol response to hypoglycemia, and at times, grossly reduced basal cortisol secretion.
- Severe forms of this functional defect may be misinterpreted as adrenal insufficiency as the etiology of hypoglycemia. The abnormal HPA axis, however, recovers completely after varying periods once hypoglycemia is strictly avoided.
- Such defect may warrant steroid replacement with the provision of stress doses in some cases of insulinoma before surgery and during the perioperative period to avoid case fatality.

References

1. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009;94(3):709–728. DOI: 10.1210/jc.2008-1410.
2. Erturk E, Jaffe CA, Barkan AL. Evaluation of the integrity of the hypothalamic-pituitary-adrenal axis by insulin hypoglycemia test. J Clin Endocrinol Metab 1998;83(7):2350–2354. DOI: 10.1210/jcem.83.7.4980.
3. Chang YH, Hsieh MC, Hsin SC, et al. Insulinoma-associated transient hypothalamus–pituitary–adrenal axis impairment and amelioration by steroid therapy and surgical intervention: A case report. Kaohsiung J Med Sci 2007;23(10):526–530. DOI: 10.1016/S1607-551X(08)70011-1.
4. Fountoulakis S, Malliopoulos D, Papanastasiou L, et al. Reversal of impaired counterregulatory cortisol response following diazoxide treatment in a patient with non insulinoma pancreatogenous hypoglycemia syndrome: Case report and overview of pathogenetic mechanisms. Hormones (Athens) 2015;14(2):305–311. DOI: 10.14310/horm.2002.1516.
5. Freda PU, Beckers AM, Katznelson L, et al. Pituitary incidentaloma: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2011;96(4):894–904. DOI: 10.1210/jc.2010-1048.
6. Benson L, Ljunghall S, Akerstrom G, et al. Hyperparathyroidism presenting as the first lesion in multiple endocrine neoplasia type 1. Am J Med 1987;82:731–737. DOI: 10.1016/0002-9343(87)90008-8.

7. Newey PJ, Thakker RV. Multiple endocrine neoplasia. In: Melmed S, Auchus RJ, Goldfine AB, et al. (Eds.). Williams Text Book of Endocrinology, 14th Edition. Philadelphia: Elsevier; 2020. pp. 1622–1657.
8. McKeeby JL, Li X, Zhuang Z, et al. Multiple leiomyomas of the esophagus, lung, and uterus in multiple endocrine neoplasia type 1. Am J Pathol 2001;159(3):1121–1127. DOI: 10.1016/s0002-9440(10)61788-9.
9. Mitrakou A, Fanelli C, Veneman T, et al. Reversibility of unawareness of hypoglycemia in patients with insulinomas. N Engl J Med 1993;329(12):834–839. DOI: 10.1056/NEJM199309163291203.
10. Kelly A, Tang R, Becker S, et al. Poor specificity of low growth hormone and cortisol levels during fasting hypoglycemia for the diagnoses of growth hormone deficiency and adrenal insufficiency. Pediatrics 2008;122(3):e522–e528. DOI: 10.1542/peds.2008-0806.
11. Welt CK, Kinsley BT, Simonson DC. Recurrent hypoglycemia does not impair the cortisol response to adrenocorticotropin infusion in healthy humans. Metabolism 1998;47(10):1252–1257. DOI: 10.1016/s0026-0495(98)90332-8.
12. McCrimmon RJ. Update in the CNS response to hypoglycemia. J Clin Endocrinol Metab 2012;97(1):1–8. DOI: 10.1210/jc.2011-1927.
13. Yadav TC, Bhutani J, Upadhyay M, et al. Recurrent hypoglycemia: An unusual finding of hypothyroidism. Thyroid Res Pract 2017;14:127–129. DOI: 10.4103/trp.trp_35_17.