Endocrinology, Diabetes & Metabolism CASE REPORTS

P Gupta and others | Pediatric insulinoma

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# Insulinoma in an adolescent female with weight loss: a case report and literature review on pediatric insulinomas

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## Summary

Insulinomas are a rare cause of persistent hypoglycemia in a previously healthy child. In addition to symptoms of hypoglycemia, individuals with insulinomas usually present with a history of incessant caloric intake and weight gain due to a constant need to counter hypoglycemia. In addition to an extensive review of the literature, we report the first case of an insulinoma coexisting with reduced appetite secondary to anorexia nervosa in an adolescent female.

### Learning points:

- Eliciting a detailed family history is important in hypoglycemia cases.
- Obtaining a thorough dietary intake, weight history, and menstrual cycles (in females) and considering a psychiatric consultation for an eating disorder when indicated.
- Although rare in the pediatric population, multiple endocrine neoplasia type 1 syndrome should be considered in the evaluation of children and adolescents with hypoglycemia who also have a family history of pituitary, pancreatic, and/or parathyroid endocrinopathies.

## Background

Insulinomas are an extremely rare cause of hypoglycemia and can be a challenging diagnosis in the pediatric age group. It is uncommon in adults with an incidence of four cases per million per year (1). In the pediatric population, the incidence is unknown but assumed to be lower in adults. In addition to the biochemical findings of non-ketotic hypoglycemia with associated elevated insulin and C-peptide levels, individuals with insulinomas commonly exhibit the classic symptoms of hypoglycemia including increased adrenergic activity (anxiety, tremulousness, palpitation, sweating, nausea, and hunger) and/or neuroglycopenic symptoms (confusion, seizures, focal neurologic deficit, and coma). An individual with an insulinoma may present with increased body weight due to the increased amount of carbohydrates consumed to prevent or counter hypoglycemia. We report the case of an adolescent female who presented with hypoglycemia due to an insulinoma and as part of the multiple endocrine neoplasia type 1 syndrome (MEN 1). Based on our review of the literature, we report the first case of an insulinoma in an adolescent presenting with hypoglycemia, weight loss, and anorexia.

## Case presentation

A previously healthy 14-year-old female of South Asian descent presented initially to her local emergency department (ED) in Guyana, South America, with

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syncopal episodes, nausea, fatigue, diplopia, and weight loss. There was no history of neonatal hypoglycemia. Her blood glucose (BG) was less than normal, but no diagnosis was made. She monitored her capillary BG at home with a glucometer whether she developed symptoms of hypoglycemia as instructed. For BG levels < 70 mg/dL, she drank beverages rich in sucrose and/or fructose. Despite performing daily BG monitoring and correcting for hypoglycemia, her frequent hypoglycemia and diplopia persisted. During the first month of BG monitoring, she experienced low BG levels approximately twice a week.

The following month, the family traveled to the United States to visit relatives, and hypoglycemia episodes increased in frequency. Due to daily episodes of hypoglycemia, along with symptoms of weakness, jitteriness, and headaches, she presented to the ED. She was alert and oriented but had tremors of her hands bilaterally. Her vital signs were normal, as was the remainder of her physical exam. Her anthropometric findings included weight 43.9 kg (8th percentile), height 157 cm (20th percentile), and BMI 17.8 kg/m$^2$ (10th percentile). Her non-fasting capillary BG (28 mg/dL) was severely low prompting the collection of a critical blood sample prior to administration of dextrose. She received a 2 mL/kg bolus infusion of 10% dextrose, and within 30 min, her BG improved to 80 mg/dL. She was admitted to the endocrinology service and received continuous dextrose-containing i.v. fluid that was titrated to maintain her capillary BG in the 100–150 mg/dL range. The patient denied use or access to illicit drugs, oral anti-hyperglycemic agents, exogenous insulin, alcohol, or any other medical therapy associated with hypoglycemia (i.e. beta-blocker, salicylates, valproic acid, etc.).

Despite the original instructions she received in Guyana for treating hypoglycemia with simple carbohydrate intake and prevention with frequent meals and snacks, she reported a concern regarding weight gain. This concern had been present for approximately 6 months prior to her original presentation and was a result of her believing that she was 'too heavy'. She admitted to eating smaller meals and restricted portion sizes during this period; however, she denied ever fasting for more than 8 h. With her limited caloric intake, she reported a 10-pound weight loss. She reached menarche at 12 years and her menstrual periods were irregular (occurring every 2 months) during the first year. However, her periods became even less frequent (occurring only twice) in the subsequent 6 months. She denied vomiting, vision loss, headaches, or galactorrhea.

Her family history was remarkable for her paternal grandfather who underwent a parathyroidectomy for the treatment of hypercalcemia. He did not have any other known hormone-related abnormalities. Her father had clusters of raised, tan-appearing lesions over his torso, but he never sought medical attention for them. He also reported a history of kidney stones, but he claimed to have normal calcium levels.

## Investigation

The critical sample revealed hypoglycemia (serum BG 32 mg/dL), hypoketosis (serum beta-hydroxybutyrate 0.1 mmol/dL), elevated insulin (13.8 µIU/mL), and elevated C-peptide (5.5 ng/mL). Growth hormone, cortisol, free fatty acid, acylcarnitine, and urine organic acid levels were within normal limits. A provisional diagnosis of endogenous hyperinsulinism was made, most likely secondary to an insulinoma, given her age and acute presentation.

An abdominal MRI revealed a 1.2 cm ovoid, well-demarcated, heterogeneously enhancing lesion along the superior aspect of the distal pancreatic body without dilatation of the pancreatic duct. There was no evidence of lymphadenopathy or distant metastasis (Fig. 1A).

## Treatment

After completion of her biochemical and imaging evaluation, and ensuring stabilization of her BG level, she underwent a minimally invasive pancreatic enucleation surgery. She tolerated the surgery well and without complications. Staining of the pancreatic specimen with anti-insulin antibody (Fig. 1B) confirmed insulinoma and excluded other functioning (glucagonoma, gastrinoma, somatostatinoma, or vasointestinal peptide tumor (VIPoma)) and non-functioning tumors.

## Outcome and follow-up

Within 24 h after surgery, fasting (80–99 mg/dL) and 2-h post-prandial (80–140 mg/dL), capillary BG levels

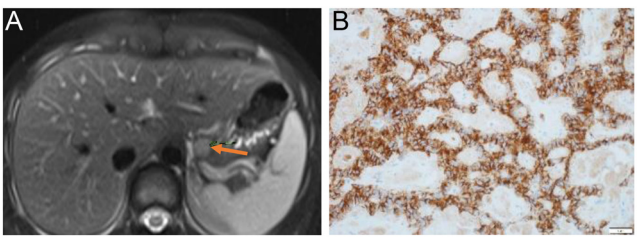


**Figure 1**
Insulinoma. (A) Pancreatic lesion on T2-weighted MRI image (arrow). (B) Tumor cells stained positive for insulin under a light microscope (magnification power, 40×).

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remained in the normal range. She reported no symptoms of tremulousness, weakness, palpitations, sweating, headaches, or confusion. Due to her aforementioned preoccupation with weight gain, the concern for a coexisting condition of anorexia nervosa prompted consultation with the Child and Adolescent Psychiatry team, who confirmed the diagnosis and prescribed a daily caloric intake goal (2000 kcal/day), serotonin-uptake inhibitor therapy, and outpatient therapy.

Given her family history concerning MEN1, a more extensive hormonal evaluation in addition to genetic testing was then performed. Her adrenocorticotropic hormone, albumin, calcium, insulin-like growth factor 1 (IGF-1), parathyroid hormone (PTH), and thyroid-stimulating hormone levels were normal, but her prolactin level (133.1 ng/dL; normal 4.2–23.0 ng/dL) was elevated. An MRI of the brain demonstrated a focal area of enhancement along the right side of the pituitary gland, consistent with a microadenoma (Fig. 2). Genetic testing for the *MEN1* gene revealed a heterozygous genetic alteration in the menin gene (C.35 C >T). Due to the autosomal dominant nature of MEN1, her first-degree relatives were subsequently screened for the mutation. Despite having no signs or symptoms of pituitary or pancreatic abnormalities, her father was of particular interest due to his kidney stones, other family history for hyperparathyroidism, and his skin lesions, although he had no signs or symptoms of pituitary or pancreatic disease. Ultimately, he was discovered to have the same mutation, and evaluation in the dermatology clinic established that his skin lesions were consistent with collagenomas.

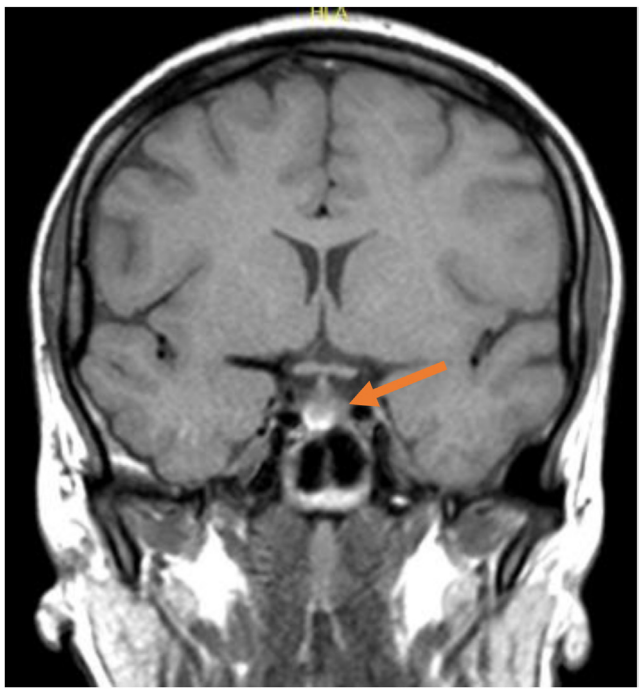

**Figure 2**
Coronal section of the MRI brain showing a pituitary microadenoma just above the Sella turcica (arrow).

Nearly 10 months after presentation, and still reporting oligomenorrhea, she denied galactorrhea, bone pain, or symptoms of hypoglycemia. Her calcium (11.8 mg/dL), PTH (86.8 pg/mL), and prolactin (202 ng/dL) levels all increased. She underwent subtotal parathyroidectomy to reduce her PTH and calcium levels and began cabergoline therapy to reduce prolactin production. Within 2 months, her calcium and PTH levels improved, and her menstrual cycles became more regular.

## Discussion

With a median age of 50 years, insulinomas are extremely rare in children. Most insulinomas are solitary, sporadic, and benign. However, 10% occur as part of MEN1, and overall, 10% are malignant (1). In addition to pancreatic tumors, individuals with MEN1 are also at risk for pituitary tumors, parathyroid hyperplasia, and dermatologic manifestations. The MEN1 syndrome is due to a mutation in the *MEN1* gene that encodes the protein menin and has an autosomal dominant mode of inheritance with high penetrance. Genetic testing is the gold standard for establishing the diagnosis of MEN1 (2). Annual screening for tumors associated with MEN1 includes the collection of plasma levels of calcium and PTH (parathyroid hyperplasia); IGF-1 (growth hormone-producing tumor); prolactin (prolactinoma); fasting insulin and glucose (insulinoma); gastrin (gastrinoma); glucagon (glucagonoma); VIP (VIPoma); pancreatic polypeptide; and chromogranin A. In addition, an MRI of the pituitary gland should be performed every 3–5 years (2).

Individuals with insulinomas commonly report adrenergic symptoms, including anxiety, tremulousness, palpitations, sweating, and hunger as well as neuroglycopenic symptoms such as confusion, seizures, and focal neurologic deficits (3, 4). In response to hypoglycemia, individuals with insulinomas are usually hungry, ingest excessive amounts of carbohydrate, and therefore, gain significant weight.

Despite the number of available biochemical studies, a clear consensus for diagnostic testing is lacking. Due to the small size of most insulinomas, imaging techniques do not always detect these tumors (5). The Endocrine Society's clinical practice guidelines suggest the diagnosis of an insulinoma in an individual with hypoglycemia

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(<55 mg/dL (3.1 mmol/L)), elevated insulin (≥18 pmol/L), and C-peptide (≥ 0.61 ng/mL) levels and suppression of β-hydroxybutyric acid (5). In the absence of confirmatory imaging evidence, the most widely used method of detection involves the calculation of an insulin–glucose ratio based on serial glucose and insulin levels after 72-h fast (6). An abnormally elevated ratio (>53.6 pmol/L/mmol/L) at 72 h provides the most sensitive (94%) and specific (89%) approach for making the diagnosis of an insulinoma (7).

After establishing the diagnosis of an insulinoma, imaging studies such as ultrasound, CT, and magnetic resonance image (MRI) of the abdomen may help localize the tumor (8). If an insulinoma is visualized, the preferred treatment is enucleation of the tumor (9).

Our patient's lack of appetite and weight loss were atypical for an insulinoma. Only after additional discussion with the patient regarding her eating habits, did it become apparent that she had a restrictive eating pattern and fear of weight gain. This ultimately led to a confirmed diagnosis of anorexia nervosa that helped to explain her lack of expected weight gain despite having an insulinoma.

Another unique feature of her presentation was oligomenorrhea. With her elevated prolactin and pituitary microadenoma, it was unclear whether the underlying cause of her menstrual irregularities was due to hyperprolactinemia or anorexia nervosa with anovulation. The fact that her menses became more regular with cabergoline therapy favored hyperprolactinemia. Our patient's family history, with her paternal grandfather's hyperparathyroidism and father's skin lesions, suggests that the insulinoma was not isolated, but rather a component of MEN1, and confirmed with genetic testing that identified the *MEN1* gene mutation.

**Table 1** Pediatric and adolescent insulinomas.

| Case# | Age (years)/sex(M/F) | Weight gain | Hunger | MEN1 syndrome | Medical issues |
|---|---|---|---|---|---|
| 1 | 8/M | NS | NS | N | N |
| 2 | 10/M | NS | NS | N | Malignant insulinoma |
| 3 | 15/M | Y | Y | N | N |
| 4 | 3/F | NS | NS | N | N |
| 5 | 5/M | NS | NS | Y | Parathyroid adenoma |
| 6 | 7/M | NS | NS | Y | N |
| 7 | 8/F | NS | NS | N | N |
| 8 | 8/M | NS | NS | N | N |
| 9 | 10/F | NS | NS | N | N |
| 10 | 13/F | NS | NS | N | N |
| 11 | 13/F | NS | NS | N | N |
| 12 | 15/M | NS | NS | N | N |
| 13 | 13/M | Y | Y | N | N |
| 14 | 11/M | Y | Y | N | N |
| 15 | 10/ M | Y | Y | NS | N |
| 16 | 9/F | Y | NS | NS | N |
| 17 | 11/F | Y | NS | NS | N |
| 18 | 14/F | NS | NS | NS | N |
| 19 | 9/F | Y | Y | Y | N |
| 20 | 9/F | Y | Y | N | N |
| 21 | 11/M | N (Loss) | Y | N | Mental retardation |
| 22 | 10/M | Y | NS | N | Trisomy 21 |
| 23 | 10/M | Y | NS | N | N |
| 24 | 15/F | Y | NS | N | N |
| 25 | 9/F | NS | NS | NS | N |
| 26 | 16/M | NS | NS | N | N |
| 27 | 14/F | NS | NS | Y | Parathyroid adenoma |
| 28 | 12/F | Y | NS | Y | Prolactinoma |
| 29 | 10/M | NS | NS | N | N |
| 30 | 11/M | NS | NS | NS | N |
| 31 | 14/F | NS | NS | Y | Glucagonoma |
| 32 | 7/M | NS | NS | N | N |
| 33 | 14/F | N (Loss) | N | Y | Prolactinoma; anorexia nervosa |

F, female; M, male; N, no; NS, not specified; Y, yes.

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In our review of the literature over the past 50 years, we identified only 32 other cases involving a child or adolescent with an insulinoma (Table 1). Including our case, weight change (14 cases), hunger (8 cases), and associated MEN1 (27 cases) were reported. One case involved a malignant insulinoma (case #2, Table 1) and seven cases were associated with MEN1. We were able to identify only one other case in which a patient presented with hypoglycemia and weight loss (case #21, Table 1), unlike our patient who experienced significant hunger (10). We were not able to identify any case reports of children, adolescents, or adults, in which a patient had both an insulinoma and anorexia nervosa.

Similar to adults**,** insulinomas in children and adolescents usually, but not always, present with increased carbohydrate intake and significant weight gain. This case outlines the importance of taking a thorough dietary, psychological, and family history on any child or adolescent presenting with hypoglycemia.

**Declaration of interest**
Drs. Gupta, Loechner, Patterson, and Felner have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. No part of the study, including study design, writing of the report, and the decision to submit the manuscript for publication, has been sponsored. No honorarium, grant, or other forms of payment was given to anyone to produce the manuscript.

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**Patient consent**
Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/parent/guardian/relative of the patient.

**Author contribution statement**
All authors took care of the patient at one point during the patient's hospitalization and all authors contributed to the editing of the manuscript.

## References

1 Service FJ, McMahon MM, O'Brien PC & Ballard DJ. Functioning insulinoma-incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clinic Proceedings* 1991 **66** 711–719. (https://doi.org/10.1016/s0025-6196(12)62083-7)
2 Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F, Brandi ML, *et al.* Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 2990–3011. (https://doi.org/10.1210/jc.2012-1230)
3 Towler DA, Havlin CE, Craft S & Cryer P. Mechanism of awareness of hypoglycemia. Perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. *Diabetes* 1993 **42** 1791–1798. (https://doi.org/10.2337/diab.42.12.1791)
4 Hepburn DA, Deary IJ, Frier BM, Patrick AW, Quinn JD & Fisher BM. Symptoms of acute insulin-induced hypoglycemia in humans with and without IDDM: factor-analysis approach. *Diabetes Care* 1991 **14** 949–957. (https://doi.org/10.2337/diacare.14.11.949)
5 Dauben L, Simon MC, Strassburger K, Burkart V, Weber KS, Schinner S, Roden M & Müssig K. Comparison of the diagnostic accuracy of the current guidelines for detecting insulinoma. *European Journal of Endocrinology* 2019 **180** 381–386. (https://doi.org/10.1530/EJE-18-0879)
6 Nauck MA & Meier JJ. Diagnostic accuracy of an 'amended' insulin-glucose ratio for the biochemical diagnosis of insulinomas. *Annals of Internal Medicine* 2012 **157** 767–775. (https://doi.org/10.7326/0003-4819-157-11-201212040-00004)
7 Thompson M, Hogg P, De Paoli A & Burgess J. Parental multiple endocrine neoplasia type 1 (MEN 1) is associated with increased offspring childhood mortality. *Journal of Clinical Endocrinology and Metabolism* 2020 **105** 231. (https://doi.org/10.1210/clinem/dgz231)
8 Peranteau WH, Palladino AA, Bhatti TR, Becker SA, States LJ, Stanley CA & Adzick NS. The surgical management of insulinomas in children. *Journal of Pediatric Surgery* 2013 **48** 2517–2524. (https://doi.org/10.1016/j.jpedsurg.2013.04.022)
9 van Beek DJ, Nell S, Verkooijen HM, Borel Rinkes IHM, Valk GD, (on behalf of the DutchMEN study group), Vriens MR & International MEN1 Insulinoma Study Group. Surgery for multiple endocrine neoplasia type 1-related insulinoma: long-term outcomes in a large international cohort. *British Journal of Surgery* 2020 **107** 1489–1499. (https://doi.org/10.1002/bjs.11632)
10 Miron I, Diaconescu S, Aprodu G, Ioniuc I, Diaconescu MR & Miron L. Diagnostic difficulties in a pediatric insulinoma: a case report. *Medicine* 2016 **95** e3045. (https://doi.org/10.1097/MD.0000000000003045)

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