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Insulinoma as the First Manifestation of MEN1: A Case of a 13-Year-Old Boy Presenting with Generalized Seizure and Hypoglycemia

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Abstract

Hypoglycemia, a widespread metabolic complication in children, has harmful impacts on normal brain function and can progress to symptomatic seizures. This report describes a rare case of a 13-year-old male who presented with a generalized tonic-clonic seizure due to severe hypoglycemia. Further diagnostic workup with a PET/CT scan revealed an insulin-secreting pancreatic tumor and a diagnosis of Multiple Endocrine Neoplasia Type 1 (MEN1) was established based on genetic testing results. The patient underwent successful distal pancreatectomy, resulting in the normalization of blood glucose levels and resolution of symptoms. The primary aim of this report is to emphasize that seizures can be a key sign of insulinomas and MEN1 syndrome in children, despite the rarity of these conditions.

Key Words: Hypoglycemia, Insulinoma, MEN1, Pediatric.

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1- INTRODUCTION

In contrast to adults, insulinomas in children are exceedingly rare functioning neuroendocrine tumors, occurring at a rate of about 1-3 cases per million per year, and are capable of causing persistent hypoglycemia (1). Most insulinomas are solitary, localized, and benign and they occur more commonly in adults; however, children show a higher proportion of non-sporadic tumors associated with Multiple Endocrine Neoplasia Type 1 (MEN1) (2-4).

Hypoglycemia accompanied by neuroglycopenic symptoms that are promptly relieved by glucose administration, known as the Whipple triad, is the fundamental diagnostic criterion for insulinoma (5). For biochemical confirmation, assessment of insulin, proinsulin, C-peptide, and blood glucose levels during hypoglycemia is required (6).

MEN1 is an uncommon autosomal dominant disorder marked by a tendency to develop tumors primarily in the parathyroid glands, the anterior pituitary, and pancreatic islet cells (7). Hyperparathyroidism presents first in about 85% of MEN1 patients. Seizures resulting from insulinoma-induced hypoglycemia are an uncommon and often misleading initial presentation, usually leading to misdiagnosis and ineffective antiepileptic treatment that fails to address the underlying metabolic cause (8, 9).

Here, we report a pediatric case with neuroglycopenia symptoms where a seizure was the first manifestation of a MEN1-related insulinoma. We hope this case prompts pediatricians to keep a vigilant eye on insulinoma for unexplained seizures associated with hypoglycemia in children.

2- CASE PRESENTATION

A 13-year-old boy with well-controlled major depressive disorder was brought to the emergency department following his first generalized tonic-clonic seizure at home shortly after breakfast. The event began with a sudden loss of consciousness, a fall, upward gaze and bilateral upper limb tonic movements lasting about 2 minutes. At the time of admission, vital signs were stable and he was in a postictal state. He was afebrile and reported no history of head trauma, incontinence or cyanosis. He was born at 28 weeks' gestation via cesarean section due to premature rupture of membranes and was hospitalized in the neonatal intensive care unit neonatal intensive care unit (NICU) for 2 months. He had been treated with sertraline 50 mg daily for MDD, which had been discontinued one month prior to arrival. Family history was positive for pancreatic cancer in his father, who died at age 35, and a pancreatic mass associated with hypoglycemia in a paternal aunt. Physical examination and review of systems revealed no significant abnormality.

Point-of-care blood glucose was 40 mg/dL (normal >70 mg/dL). Infusion of 10% dextrose and intravenous diazepam was initiated. Electrolytes, metabolic panel, VBG, lactate, ammonia and thyroid function tests were within normal limits. A critical sample collected during hypoglycemia revealed an insulin level of 12 µIU/mL (normal <6 µIU/mL) and C-peptide level of 3.2 ng/mL (normal 0.5 - 2.0 ng/mL) which were inappropriately elevated for hypoglycemia. Urine toxicology was negative. Electroencephalography showed epileptiform discharges. Brain Magnetic resonance imaging (MRI) without contrast revealed a nonspecific hyperintensity at periventricular white matter of peri trigonal areas, with no structural abnormalities of the pituitary gland. A low morning cortisol level of 3 µg/dL (normal

5-25 µg/dL) prompted further evaluation; However, a standard high-dose Synacthen stimulation test with 250 µg of synthetic ACTH demonstrated a 30-minute post-injection peak cortisol level of 20 µg/dL (normal ≥18 µg/dL).

Under euglycemic and nutritionally stable conditions, serum insulin-like growth factor-1 (IGF-1) was low at 102 ng/mL (reference range 120–360 ng/mL). Subsequently, growth hormone stimulation testing with oral clonidine (0.15 mg/m², approximately one 200 µg tablet for this child) revealed an inadequate response, with a peak GH level of 5.4 ng/mL at 60 minutes (normal ≥7–10 ng/mL). This may lead us to partial anterior pituitary involvement. Abdominal ultrasonography showed several mesenteric lymph nodes, with the largest one measuring 10 mm. Further diagnostic imaging with 68Ga-DOTATATE PET/CT scan demonstrated an increased uptake measuring 1.0 × 0.9 × 0.8 cm in the tail of the pancreas, highly suggestive of insulinoma (Figure 1).

Considering pituitary dysfunction and insulinoma together, we thought of MEN syndromes. Whole-exome sequencing (WES) was then performed, which revealed a pathogenic heterozygous mutation in the MEN1 gene, confirming the diagnosis of MEN1. Treatment with diazoxide achieved partial control of blood glucose; However, glucose fluctuations persisted. Due to confirmed focal insulinoma, poor glucose control and MEN1 status, the patient underwent near-total distal pancreatectomy without complications. Pathology confirmed a well-differentiated pancreatic neuroendocrine tumor (WHO Grade 2) with a Ki67 proliferation index of up to 18%, capsular invasion, and foci of exocrine parenchymal necrosis, consistent with insulinoma. During a six-month follow-up, blood glucose levels were consistently stable over 100 mg/dL, and no further hypoglycemic episodes occurred; thus, diazoxide was discontinued. Genetic screening of first-degree relatives detected the same MEN1 mutation in his asymptomatic younger sister. Although genetic testing was not available for the deceased father and paternal aunt, their clinical histories suggest an inherited predisposition to MEN1-associated pancreatic neuroendocrine tumors.

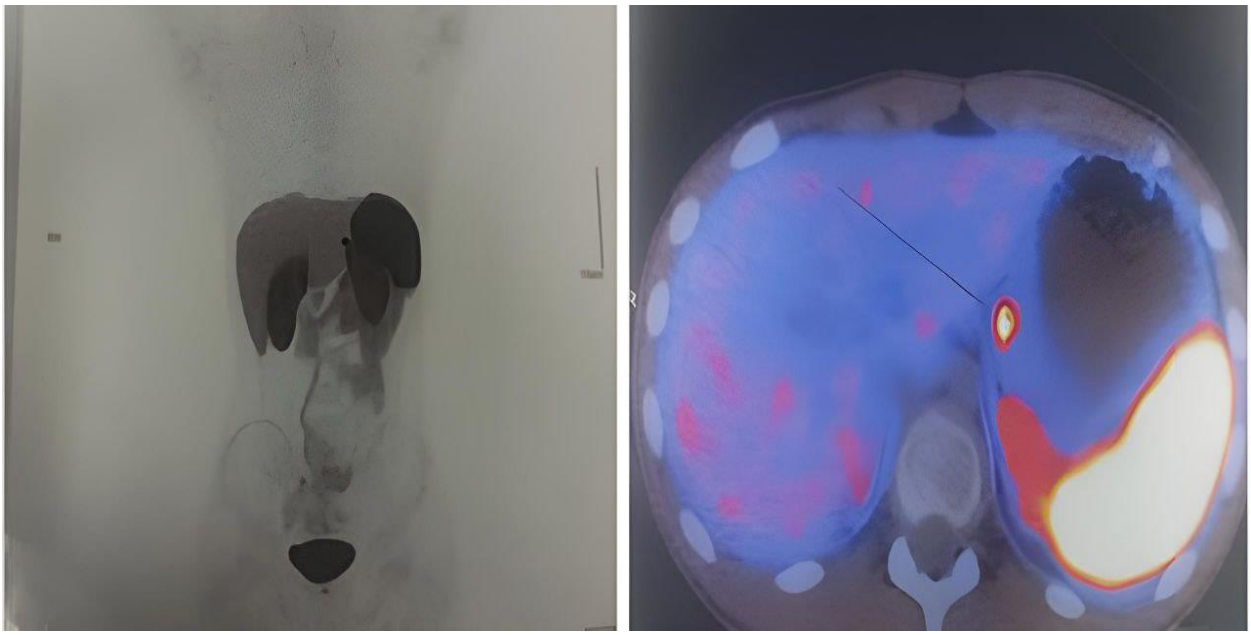

Figure-1: The 68Ga-DOTATATE PET/CT scan revealed a focal DOTA activity, likely corresponding to the pancreatic body/tail, most plausibly representing the source of the patient's known hyperinsulinemia.

3- DISCUSSION

Unlike infancy, hypoglycemia in children is uncommon. However, when accompanied by hyperinsulinemia, our differential diagnosis includes factitious cases due to exogenous insulin, congenital hyperinsulinism (CHI), pancreatic beta cell hyperplasia (nesidioblastosis), insulinoma and other endocrine disorders like adrenal insufficiency or hypopituitarism (4, 8, 10). In our patient, factitious hyperinsulinism was excluded due to a lack of access to exogenous insulin. Although CHI and insulinoma may present with similar biochemical findings, the presence of a pancreatic mass on CT scan, the confirmed MEN1 mutation, and the patient's older age compared to typical CHI cases collectively support a diagnosis of insulinoma. The patient's adequate cortisol response in the standard high-dose Synacthen test excluded adrenal insufficiency and indicated that the initial low cortisol level was likely transient and related to acute hypoglycemia. Although pituitary MRI findings were unremarkable, abnormal IGF-1 levels and an inappropriate response to the clonidine stimulation test suggested isolated pituitary dysfunction.

Insulinomas are the most common cause of hyperinsulinemic hypoglycemia in older children and adults, and clinicians should consider MEN1 (Wermer syndrome) in such cases. MEN1 markedly increases the risk of pancreatic tumor recurrence and metastasis, reported in up to 40% of patients with insulinoma (11). In our patient, concomitant pituitary dysfunction and insulinoma, and suspicion for MEN1 led to genetic testing which confirmed the diagnosis. Family screening revealed the same predisposing mutation in his asymptomatic sister, emphasizing the importance of early genetic evaluation in at-risk relatives.

Given the multisystem involvement and higher recurrence of endocrine neoplasms in MEN1, it is also important to monitor the patient for additional endocrine neoplasms from childhood (4, 12, 13). MEN1 usually manifests as hyperparathyroidism, while pancreatic and pituitary tumors are less common; in this patient, the first presentation was an insulinoma (14).

Management of insulinoma includes both medical and surgical approaches. Medical therapy with diazoxide can offer a temporary solution by inhibiting insulin secretion. While the size threshold for surgical removal is argued and surgery may lead to serious complications such as postoperative diabetes, it continues to be the preferred curative approach for localized tumors (15, 16). In our case, persistent blood glucose fluctuations necessitated enucleation of the pancreatic tumor.

Previous studies have also documented similar neurological symptoms in children, including bizarre movements and seizures, which were initially misinterpreted but later diagnosed as endogenous hyperinsulinism secondary to an insulinoma of the pancreas (1, 11, 17, 18). In some instances, patients were ineffectively treated with anti-epileptic drugs for a long time before a diagnosis of insulinoma was ultimately made (9, 19). Unlike adults with well-known diagnostic criteria for insulinoma, the diagnosis of this issue is delayed until aging pediatrics present with neurologic symptoms. This case highlights that recurrent hypoglycemia-induced seizures in pediatric patients should prompt evaluation for endocrine and metabolic causes to prevent long-term neurologic injury.

4- CONCLUSION

Early recognition of insulinoma and underlying MEN1 syndrome in pediatric patients presenting with seizures and hypoglycemia can lead to appropriate diagnosis and curative treatment. This case

emphasizes the need for a multidisciplinary approach, including endocrine, genetic, and surgical evaluation in rare pediatric presentations like this.

5- PATIENT CONSENT

Written informed consent was obtained from the patient's legal guardian for the publication of this case report and accompanying images.

6- CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

7- FUNDING

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