Cite as: Kamińska-Jackowiak O, Kordek J, Stefanowicz M, Chobot A: Neuroglycopaenia as the first manifestation of MEN1 syndrome.
Pediatr Med Rodz 2024; 20 (2): 238–241

Olga Kamińska-Jackowiak[1,2], Justyna Kordek[3],
Marek Stefanowicz[4], Agata Chobot[1,2]

Received: 08.11.2023
Accepted: 04.04.2024
Published: 27.09.2024

Neuroglycopaenia as the first manifestation of MEN1 syndrome

Neuroglikopenia jako pierwsza manifestacja zespołu MEN1

[1] Department of Paediatrics, Institute of Medical Sciences, University of Opole, Opole, Poland
[2] Department of Paediatrics, University Clinical Hospital in Opole, Opole, Poland
[3] Student Scientific Association of Paediatrics, Faculty of Medicine, University of Opole, Opole, Poland
[4] Department of Paediatric Surgery and Organ Transplantation, The Children's Memorial Health Institute, Warsaw, Poland
Correspondence: Olga Kamińska-Jackowiak, Department of Paediatrics, University Clinical Hospital in Opole, Wincentego Witosa 26, 45-401 Opole, Poland, e-mail: olga.kaminska-jackowiak@uni.opole.pl

https://doi.org/10.15557/PiMR.2024.0034

ORCID iDs
1. Olga Kamińska-Jackowiak https://orcid.org/0000-0002-4695-7225
2. Agata Chobot https://orcid.org/0000-0002-9622-4433

Abstract

Insulinoma is a neuroendocrine tumour of islet cells and a rare cause of hypoglycaemia in both adults and the paediatric population, with an incidence is 1–4 cases/million/year. Insulinoma may occur as an isolated tumour or as a component of multiple endocrine neoplasia syndrome 1. In the case presented below, a 15-year-old female patient with no significant medical history was brought to the emergency department by a medical rescue team, exhibiting symptoms of neuroglycopaenia for several hours. After excluding more common causes of hypoglycaemia, insulinoma was suspected. Given the patient's very young age at onset and a significant family history, laboratory and imaging diagnostics were performed for multiple endocrine neoplasia syndrome 1. Once more common causes have been ruled out, insulinoma should be considered in the differential diagnosis of hypoglycaemia. If the diagnosis of insulinoma is confirmed, the possibility of multiple endocrine neoplasia syndrome 1 should be considered.

Keywords: hypoglycaemia, insulinoma, multiple endocrine neoplasia type 1

Streszczenie

Insulinoma jest guzem neuroendokrynnym komórek beta wysp trzustkowych, będącym bardzo rzadką przyczyną hipoglikemii zarówno u dorosłych, jak i u dzieci (częstość występowania w populacji wynosi 1–4/mln/rok). Insulinoma może występować jako guz sporadyczny lub składowa zespołu mnogich nowotworów układu wydzielania wewnętrznego typu 1. W artykule opisano przypadek 15-letniej pacjentki bez istotnego wywiadu chorobowego przywiezionej przez zespół ratownictwa medycznego na szpitalny oddział ratunkowy z objawami neuroglikopenii, które utrzymywały się od kilku godzin. Po wykluczeniu częstszych przyczyn hipoglikemii wysunięto podejrzenie guza insulinowego, a ze względu na bardzo młody wiek zachorowania i obciążony wywiad rodzinny przeprowadzono diagnostykę laboratoryjną i obrazową w kierunku zespołu mnogich nowotworów układu wydzielania wewnętrznego typu 1. W diagnostyce różnicowej po wykluczeniu częstszych przyczyn hipoglikemii należy rozważyć guz insulinowy. Po potwierdzeniu rozpoznania insulinomy należy wziąć pod uwagę zespół mnogich nowotworów układu wydzielania wewnętrznego typu 1.

Słowa kluczowe: hipoglikemia, insulinoma, zespół mnogich nowotworów układu wydzielania wewnętrznego typu 1

INTRODUCTION

Insulinoma is a neuroendocrine tumour of pancreatic beta cells and a rare cause of hypoglycaemia in both adults and children (the incidence in the population is 1–4 cases/1 million/year)[1]. Insulinoma can occur as a sporadic tumour or as part of multiple endocrine neoplasia type 1 (MEN1). MEN1 is caused predominantly (90%) by a germline mutation in the *MEN1* gene, inherited in an autosomal dominant manner[2,3]. The mutation results in the loss of the gene's function and lack of menin protein, which predisposes individuals to the development of various tumours, including those in the parathyroid glands, pituitary gland, and the neuroendocrine system of the gastroenteropancreatic (GEP) tract. Symptoms of MEN1 may result from the hormonal activity of these tumours or from the mass effect. Hyperparathyroidism symptoms, usually occurring between the ages of 20 and 25, are most commonly the first manifestation of MEN1[2]. This article describes the case of a 15-year-old female patient with no significant medical history whose first manifestation of MEN1 was symptoms of neuroglycopaenia.

CASE REPORT

A 15-year-old female patient was transferred by the Emergency Medical Team (EMT) to the Emergency Department (ED) with symptoms of neuroglycopaenia that had persisted for several hours. The EMT found the patient conscious but without logical contact; subsequently, general seizures occurred. Based on clinical presentation and capillary blood glucose measurement, the EMT diagnosed severe hypoglycaemia and administered glucose (6 g) intravenously and glucagon (1 mg) intramuscularly. This increased the capillary blood glucose level to 196 mg/dL. Subsequently, the patient was transported to the ED. At the hospital, the patient presented with drowsiness and confusion, and another episode of hypoglycaemia was recorded (47 mg/dL). According to the patient's mother, there were no hypoglycaemic drugs in their home. In addition, the mother reported that her daughter had recently been experiencing increased fatigue and polydipsia, and had several fainting episodes without loss of consciousness. The primary care physician associated these symptoms with asthma. A detailed medical history revealed that the patient's father had died at the age of 37 from a pancreatic tumour of unknown aetiology. On the second day of the patient's hospitalisation, access to abdominal computed tomography scans of the patient's father was obtained. They revealed focal changes in the head of the pancreas and adrenal glands, and nephrolithiasis.

Despite the intravenous administration of a glucose solution, the patient's glycaemia could not be stabilised. On admission to the paediatric ward, the patient remained in moderate general condition and was drowsy. Laboratory tests were performed, including a urine toxicology test, ruling out poisoning. Computed tomography of the head with contrast was performed to exclude stroke; the image of the cerebrum was described as normal. Elevated insulin and C-peptide levels during hypoglycaemia were found, indicating endogenous hyperinsulinaemia (Tab. 1).

A continuous intravenous infusion of 10% glucose was initiated, along with a high-protein, high-fat diet. Several attempts to stop or reduce the glucose infusion were made, but each led to a recurrence of hypoglycaemia within 30 minutes, accompanied by persistently elevated insulin levels. The lack of inhibition of insulin secretion suggested an insulinoma. Given the patient's young age and ambiguous family medical history, further diagnostics for MEN1 was pursued. Laboratory tests revealed hypophosphataemia, low vitamin D levels, elevated total and ionised calcium, and increased levels of parathyroid hormone, growth hormone, and prolactin (Tab. 1). An ultrasound examination of the abdomen was performed, followed by magnetic resonance imaging, which revealed foci in the pancreas and liver of unknown aetiology. A thyroid ultrasound revealed structures consistent with a parathyroid adenoma.

The patient was transferred to the Children's Memorial Health Institute in Warsaw. Next-generation sequencing revealed a pathogenic variant in one allele of the *MEN1* gene, thereby confirming the diagnosis of MEN1. Abdominal computed tomography and scintigraphy using labelled somatostatin analogues (^{68}Ga) were performed, showing increased expression of somatostatin receptors in pancreatic foci, which indicated neuroendocrine changes. The patient underwent surgery. Two nodules were enucleated, and histopathological examination confirmed the presence of neuroendocrine tumours. In the postoperative period, episodes

Parameter (reference value)	First day of hospitalisation (day of admission)	Second day of hospitalisation
Glucose (70–100 mg/dL)	116*	47; 24
Insulin (2.6–24.9 µUI/mL)	43.14	24.73; 30.83
C-peptide (1.1–4.4 ng/mL)	6.73	6.73; 5.23
Calcium (total) (2.25–2.75 mmol/L)		2.72
Phosphorus (0.9–1.6 mmol/L)		0.74
Alkaline phosphatase (<270 U/L)		150
Vitamin D (30–80 ng/mL)		12.6
Parathyroid hormone (10–60 pg/mL)		100.6
Prolactin (4.8–23.3 ng/mL)		35.5
Growth hormone (<12 ng/mL)		78
* Result obtained after intravenous administration of glucose solution.		

Tab. 1. Results of selected laboratory tests in the patient (venous blood)

 DOI: 10.15557/PiMR.2024.0034

of hypoglycaemia (40–50 mg/dL) and pancreatic juice leakage were observed, leading to reoperation. The tail of the pancreas and another nodule in the head of the pancreas were removed. After reoperation, no further episodes of hypoglycaemia were observed. During follow-up hospitalisation, magnetic resonance imaging of the head revealed a hypointense focus (5 mm) on the right side of the anterior lobe of the pituitary gland. Ultrasound examination of the thyroid gland revealed previously detected foci corresponding to adenomas in the parathyroid glands. Laboratory tests again confirmed hyperparathyroidism. At the time of preparing this article, the patient remained under surgical and endocrinological care at the Children's Memorial Health Institute in Warsaw.

DISCUSSION

Hypoglycaemia is defined as a plasma glucose concentration <55 mg/dL[4]. In cases of hypoglycaemia in non-diabetic individuals, poisoning caused by excessive alcohol consumption, hypoglycaemic drugs (including insulin) or other medicaments, including non-selective beta-blockers, pentamidine or ACE inhibitors[4,5], should be ruled out first. Less common causes of hypoglycaemia include deficiencies in counterregulatory hormones, e.g. adrenal insufficiency, as well as conditions in which the demand for glucose exceeds its supply, gluconeogenesis or glycolysis, like end-stage liver disease, renal failure, and sepsis[5]. An occasional cause of hypoglycaemia is uncontrolled endogenous insulin production due to an insulinoma[5]. In 6–7.6% of cases, insulinoma is a component of multiple endocrine neoplasia type 1 (MEN1)[1].

MEN1 is caused predominantly (90%) by a germline mutation (up to 10% are *de novo* mutations) of the *MEN1* gene encoding menin, inherited in an autosomal dominant manner[2,3]. The most common endocrinopathy is primary hyperparathyroidism resulting from a parathyroid tumour, which usually develops between the ages of 20–25[2]. Hypercalcaemia may remain asymptomatic for a long time, or its symptoms may be nonspecific, such as chronic fatigue, muscle weakness, abdominal pain, or constipation. Over time, it may lead to nephrolithiasis, gastric ulcer disease, or age-inappropriate osteoporosis[2,3]. In the presented case, the patient's nonspecific fatigue was initially attributed to bronchial asthma. Laboratory tests performed at the beginning of the diagnostics revealed features of primary hyperparathyroidism, and an ultrasound examination raised the suspicion of parathyroid adenoma, which was confirmed through further diagnostics. Of note is the fact that nephrolithiasis was documented in the computed tomography of the patient's father shortly before his death.

The most common neuroendocrine tumour of the gastrointestinal tract in MEN1 is gastrinoma[2,3]. Insulin-secreting tumours, though rarer, are another clinical manifestation of MEN1. Excessive endogenous insulin secretion by the tumour causes hypoglycaemia, with symptoms resulting from the stimulation of the autonomic nervous system, such as hyperhidrosis, nausea, palpitations or tachycardia, as well as neuroglycopaenia. These symptoms appear during fasting, coincide with hypoglycaemia, and disappear after the administration of carbohydrates (the so-called Whipple's triad)[1]. In the presented case, the patient experienced symptoms of neuroglycopaenia each time there was an attempt to discontinue the intravenous glucose infusion, accompanied by hypoglycaemia, hyperinsulinemia, and elevated C-peptide levels.

Other tumours associated with MEN1 are pituitary tumours, the most common of which is prolactinoma[2]. Symptoms may result from uncontrolled prolactin secretion by the tumour or the mass effect on adjacent structures. In this case, there were no pituitary tumour symptoms, and the prolactin and growth hormone levels were within the age norm. However, magnetic resonance imaging of the head revealed a focus in the anterior pituitary gland. This lesion remains under observation.

The diagnosis of MEN1 is based on the finding of ≥2 disorders characteristic of MEN1, ≥1 disorder in a patient with a positive family history of MEN1, or detecting a mutation in the *MEN1* gene in an asymptomatic individual[3]. In this case, next-generation sequencing was performed, revealing a mutation in one allele of the gene, which is sufficient for the occurrence of symptoms in cases of autosomal dominant inheritance[3].

The treatment of neoplasms in MEN1 syndrome is the same as in the case of sporadic tumours. Difficulties result mainly from the multifocal nature of the changes and more frequent relapses. The treatment of choice for insulinoma is tumour resection[6,7]. For symptomatic hyperparathyroidism, the gold standard is subtotal or total parathyroidectomy[3,7]. If the procedure is ineffective, calcimimetics are used, which target the calcium receptor in the parathyroid glands and reduce the secretion of parathyroid hormone. In asymptomatic cases or laboratory hyperparathyroidism without clinical symptoms, dietary management is initiated until the decision to perform surgery is made, as was the approach for this patient. Treatment for pituitary tumours may be pharmacological, in the case of hormonally active tumours, or surgical, depending on the nature and size of the tumour[7].

CONCLUSIONS

This report aims to describe a case of MEN1 syndrome in an adolescent, the first symptom of which was neuroglycopaenia. After excluding other possible causes of hypoglycaemia in children and adolescents without diabetes, such as hypoglycaemic drug poisoning or alcohol abuse, rare diseases like insulinoma should be considered. In cases where insulinoma is suspected, a thorough family medical history should be obtained regarding MEN1 syndrome. Detailed laboratory tests and medical imaging should be performed, which allow for the assessment of the functions of the endocrine glands.

DOI: 10.15557/PiMR.2024.0034

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Author contribution

Writing of manuscript: OKJ, JK, MS. Critical review of manuscript: AC. Final approval of manuscript: OKJ, AC.

References

1. Zhuo F, Anastasopoulou C: Insulinoma. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL 2024–.
2. Giusti F, Marini F, Brandi ML et al.: Multiple endocrine neoplasia type 1. In: Adam MP, Feldman J, Mirzaa GM et al. (eds.): GeneReviews® [Internet]. University of Washington, Seattle, WA 1993–2024.
3. Kamilaris CDC, Stratakis CA: Multiple endocrine neoplasia type 1 (MEN1): an update and the significance of early genetic and clinical diagnosis. Front Endocrinol (Lausanne) 2019; 10: 339.
4. Bansal N, Weinstock RS: Non-diabetic hypoglycemia. In: Feingold KR, Anawalt B, Blackman MR et al. (eds.): Endotext [Internet]. MDText.com, Inc., South Dartmouth 2000–.
5. Mathew P, Thoppil D: Hypoglycemia. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL 2024 Jan–.
6. van Beek DJ, Nell S, Verkooijen HM et al.: Surgery for multiple endocrine neoplasia type 1-related insulinoma: long-term outcomes in a large international cohort. Br J Surg 2020; 107: 1489–1499.
7. Singh G, Mulji NJ, Jialal I: Multiple endocrine neoplasia type 1. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL 2024 Jan–.