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CASE REPORT

Rare clinical manifestation of multiple endocrine neoplasia type 1

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Abstract

OBJECTIVE: Multiple endocrine neoplasia type 1 (MEN1) is a rare disorder characterized by tumors in various endocrine glands. It is caused by a mutation in the *MEN1* gene. This gene encodes menin, a protein that regulates cell proliferation. The clinical manifestation of the syndrome most commonly involves hyperparathyroidism and pancreatic, pituitary gland, and adrenocortical adenomas. Although the first symptoms of the disease usually occur in patients under the age of 20, the data on MEN1 in children is scarce. Here, we report a case study of a familial MEN1 syndrome with a central nervous system ganglioglioma, a manifestation that has not been characterized so far.

CASE REPORT: The diagnosis of a 17-year-old boy with hypoglycemia of unknown origin revealed the presence of a pancreatic tumor. As kidney stone disease and acute pancreatitis were reported in his father, and his asymptomatic sister was initially diagnosed with a pancreatic tumor, a familial MEN1 syndrome was suspected. Indeed, a pathogenic mutation within the *MEN1* gene was detected. Further diagnosis revealed primary hyperparathyroidism in both children and their father, which is typical of MEN1. The girl also presented with hydrocephalus caused by ganglioglioma of the central nervous system. Surgical treatment was successfully conducted in both children.

CONCLUSIONS: The reported family case provides evidence of the diagnostic and therapeutic difficulties related to the MEN1 syndrome. In children, the benefits of an early surgery should be considered in relation to the risks of possible surgical complications and consequences of a loss of endocrine gland function.

Abbreviations:

MEN1	- multiple endocrine neoplasia type 1
MRI	- magnetic resonance imaging
CT	- computed tomography
EEG	- video electroencephalography
^{18}F-DOPA PET-CT	- fluorine-18-L-dihydroxyphenylalanine positron emission tomography-computed tomography scan
SUV	- standardized uptake value
EUS	- endoscopic ultrasound
^{99m}Tc-MIBI SPECT	- technetium-99m sestamibi single-photon emission computed tomography
GLP1 PET-CT	- ^{68}Ga glucagon-like peptide-1 positron emission tomography-computed tomography scan
G1	- well-differentiated tumor, low grade
G2	- moderately-differentiated tumor, intermediate grade
pT1	- tumor limited to mucosa and submucosa
N0	- no involved lymph nodes

INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant cancer syndrome manifested by tumors of various endocrine glands (Giusti *et al.* 2019). It occurs in 1 to 9 per 100 000 individuals and affects both sexes equally (Giusti *et al.* 2017). The syndrome is characterized by a delayed manifestation, diverse severity, and very high penetrance. No data on MEN1 prevalence in children is available (Kamilaris & Stratakis, 2019). Clinical manifestation of MEN1 may occur in childhood but rarely in individuals younger than 10 years old. In pediatric literature, mostly case study descriptions of MEN1 are shown.

The most common manifestations of MEN1 syndrome are hyperparathyroidism resulting from parathyroid hyperplasia, pancreatic endocrine tumors and adenomas of the anterior pituitary gland. Adrenocortical adenomas and gastric, thymic and bronchopulmonary neuroendocrine tumors can also occur. Other alterations which may be present in MEN1 syndrome include lipomas, leiomyomas, facial angiofibromas, collagenomas, and meningiomas (Kamilaris & Stratakis, 2019).

According to current guidelines (Thakker *et al.* 2012), MEN1 syndrome is diagnosed when at least two MEN1-associated tumors occur in a patient: hyperparathyroidism resulting from parathyroid hyperplasia, pancreatic endocrine tumor, or pituitary adenoma. Familial MEN1 is recognized if a MEN1-associated tumor is present in at least two first-degree relatives. The diagnosis might also be established in an asymptomatic individual who has not developed biochemical or radiological abnormalities but in whom a germline MEN1 mutation has been identified.

Clinical manifestations of the syndrome are associated with mutations in the *MEN1* gene, which consists of 10 exons and is located on chromosome 11q13 (Giust *et al.* 2019; Thakker *et al.* 2012). The *MEN1* gene was identified in 1997, and so far over 1300 mutations have been described. It encodes menin, a tumor suppressor protein that regulates cell proliferation. A mutation that inactivates the *MEN1* gene results in the lack of menin production by endocrine gland cells, which is, presumably, a factor inducing malignant transformation (Kamilaris & Stratakis, 2019). However, no genotype/phenotype correlation has been described so far.

Here, we present a case study of familial MEN1 syndrome with a confirmed pathogenic variant c.1233_1234delinsT, located in exon 10, in one allele of the *MEN1* gene. This case presents central nervous system ganglioglioma, a manifestation that has not been characterized so far.

CASE REPORT

A 17-year-old adolescent boy was admitted to the Clinic of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology of the Developmental Age, at the Pomeranian Medical University. For 5 years he had been examined in several other medical centers because of hypoglycemia. At the age of 12, he experienced the first incident of epileptic seizures. At that time, his blood sugar level was 3.11 mmol/L. No abnormalities were identified with medical imaging examination, including magnetic resonance imaging (MRI), computed tomography (CT), and video electroencephalography (EEG). Epilepsy was diagnosed due to recurrent tonic seizures, and valproate treatment was introduced. The patient reported malaise, sleepiness, and increased exercise intolerance. Biochemical tests conducted at the time revealed a fasting plasma glucose concentration of 2.22 mmol/L, and therefore, broad diagnostics of hypoglycemia were initialized. In a diagnostic fast test, after 19 hours of starvation, glycemia was 1.94 mmol/L, insulin concentration was 5.13 uIU/mL, and C-peptide concentration was 1.24 ng/mL. The test also revealed negative ketonuria and a low level of serum hydroxybutyric acid (Table 1). Because the insulin level was relatively high, the diagnostic fast test was repeated after 6 months. Again, despite symptomatic hypoglycemia, insulin suppression was not complete: glycemia after starvation was 2.0 mmol/L, insulin was 6.01 uIU/mL, and C-peptide was 1.37 ng/mL (Table 1). Diazoxide treatment was included, using a 200 mg evening dose, which normalized glycemia. When the patient was 15 years old, a fluorine-18-L-dihydroxyphenylalanine positron emission tomography-computed tomography scan (^{18}F-DOPA PET)-CT scan was done. It revealed metabolically active lesions in the head and uncinate process of the pancreas. The lesions were, however, not visible in the ultrasonography, MRI, or CT examinations conducted in the following years. While waiting for an endoscopic ultrasound (EUS) of the upper digestive tract, ultrasonography of the pancreas was again performed. It showed a 13-mm focal lesion near the superior mesenteric vein. This finding was confirmed with CT and EUS (Figure 1). At the same time, the patient's asymptomatic sister

Tab. 1. The results of laboratory tests obtained during diagnostic fast tests in a 13-year-old boy

	Diagnostic fast test	
	13 years	**13.5 years**
Glucose [mmol/L] (60-99)	1.94	2.0
Insulin [μIU/mL] (2.6-24.9)	5.13	6.01
C-peptide [ng/mL] (0.9-7.10)	1.24	1.37
Ketonuria	(-)	(-)
FFA (free fatty acid) [mmol/L] (0.06-0.60)	-	-
β-Hydroxybutyric acid [mmol/L] (0.03-0.65)	<0.07	-
Lactic acid [mg/dL] (4.5-19.8)	15.8	15.2
Ammonia [μg/dL] (20.0-80.0)	33.0	-
Cortisol [μg/dL] (7 am - 10 am: 6.2-19.4; 4 pm – 8 pm: 2.3-11.9)	12.3	-
Glycaemia [mg/dL] after glucagon supply	73	74
GC/MS (gas chromatography–mass spectrometry)	Valproate Small ketonuria	-

underwent ultrasonography. The examination revealed a tumor in the tail of the pancreas and stones in both kidneys. Detailed family history indicated kidney stone disease in the patient's father and acute pancreatitis. Because familial MEN1 syndrome was suspected, diagnostics tests directed to the evaluation of this disorder were performed. The initial stage of primary hyperparathyroidism, hypercalcemia with a normal level of parathyroid hormone, was recognized (Table 2). A technetium-99m sestamibi single-photon emission computed tomography (^{99}mTc-MIBI SPECT)-CT scan revealed increased tracer storage within the left inferior parathyroid gland.

The treatment of the 17-year-old boy began with the resection of the pancreatic tumor. Because of difficulties in the determination of the number and localization of the lesions, the preoperative diagnosis included ^{99}mTc-Tektrotyd (increased expression of somatostatin receptor), ^{18}F-DOPA PET-CT, and ^{68}Ga glucagon-like peptide-1 (GLP1) PET-CT (Figure 2). Three focal lesions, within the head, body and tail of the pancreas, were identified. During the surgery, 3 lesions were excised from the uncinate process, and the head/body and tail of the pancreas. Histopathological and immunohistochemical examination revealed glucagonoma G2, pT1, N0 (abbreviations refer to the tumor grading and staging: G2 – moderately-differentiated tumor, intermediate grade, pT1 – tumor limited to mucosa and submucosa, N0 – no involved lymph nodes) with a maximum dimension of 0.7 cm and a Ki67

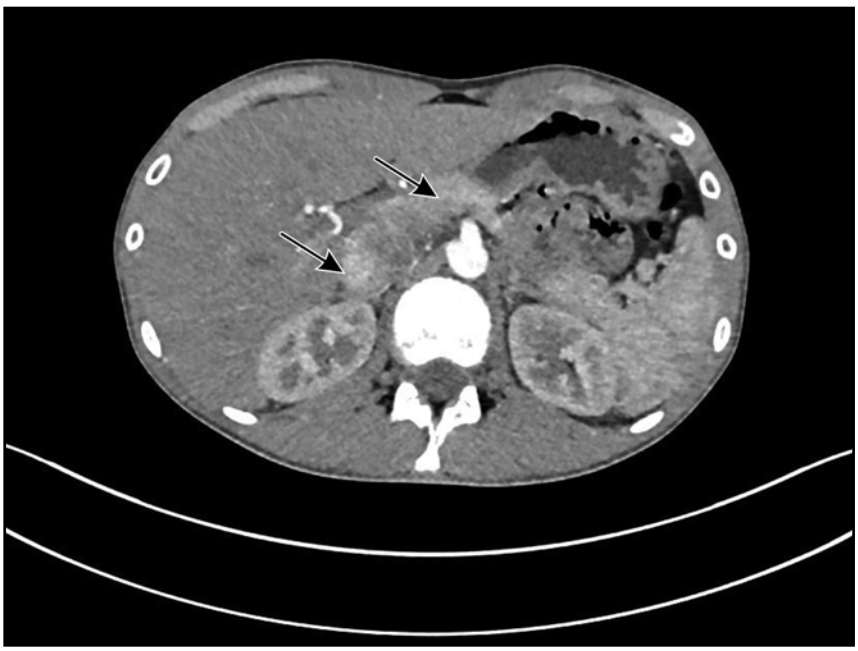

Fig. 1. CT (computer tomography) with contrast from the boy diagnosed with MEN1 (multiple endocrine neoplasia type 1) syndrome. Arrows indicate areas of mild contrast enhancement in the pancreas suggesting the presence of focal lesions.

(Ki67 antigen, marker of proliferation) proliferative index below 3%. It also revealed a glucagonoma G2, pT1, N0 with a maximum dimension of 1.1 cm and Ki67 up to 5% and an insulinoma/glucagonoma G1 (well-differentiated tumor, low grade), pT1, N0 with a maximum dimension of 1.2 cm and a Ki67 proliferative index below 3%. A postoperative leak from the tail of the pancreas caused by a structure of the pancreatic duct after removal of the centrally-located lesion was confirmed by endoscopic retrograde cholangiopancreatography with wirsungography. Therefore, a reoperation with resection of the tail of the pancreas and distal pancreatico-enteric anastomosis was conducted. Histopathological and immunohistochemical examination within the resected tail of the pancreas revealed multiple foci of neuroendocrine tumor G2, pT1, N0 with a maximum dimension of 0.5-0.6 cm, glucagon (+), and a Ki67 proliferative index up to 10%. Surgery led to normoglycemia and discontinuation of diazoxide therapy. Next, because persistent hyperplasia with an initial phase of hyperparathyroidism was confirmed in consecutive examinations, a subtotal parathyroidectomy was performed, leaving 1/3 of the left inferior parathyroid gland. This resulted in normalization of the serum calcium level.

At the same time, the patient's 14-year-old sister was diagnosed. Ultrasonography revealed a tumor 20 mm in diameter within the tail of the pancreas. After admission to the hospital, the girl did not report any ailments, and no significant abnormalities were detected in a physical examination. At the age of 7, the girl experienced renal colic incidence. At that time, ultrasonography confirmed the presence of kidney stones in the kidneys, and biochemical examination revealed an increased level of ionized calcium, but total calcium and parathyroid hormone levels were within the normal range. No recurrence of renal colic was observed in the following years. Ultrasound examination before admission to the clinic showed, apart from the pancreatic tumor, also kidney stones in both kidneys. Primary hyperparathyroidism was diagnosed (Table 3) with increased tracer storage in the right inferior parathyroid gland in ^{99}mTc-MIBI SPECT-CT. The presence of a pancreatic tumor was confirmed with CT (size 20x18x22 mm), somatostatin receptor scintigraphy with ^{99}mTc-tektreotyd, and ^{18}F-DOPA PET-CT (Figure 3). Endoscopic examination of the upper gastrointestinal tract revealed reflux esophagitis, gastro- and duodenopathy, and *Helicobacter pylori* infection. Biochemical examination did not confirm hormonal activity of the pancreatic tumor. Because the observed abnormalities were typical of MEN1 syndrome, MRI of the brain and pituitary gland was performed. This showed a central nervous system tumor located near the pineal gland and *lamina tecti*, 22x19x25 mm in size, and causing active hydrocephalus (Figure 4). It required an urgent endoscopic third ventriculostomy. The activity of the tumor was visualized by ^{18}F-DOPA PET-CT. The MRI examination also revealed lipoma of the sphenoid bone and the petrous part of the temporal bone. After the initial

Tab. 2. Results of laboratory tests of a 17-year-old boy

Parameter	Value
Cortisol [µg/dL] (7 am - 10 am: 6.2-19.4; 4 pm – 8 pm: 2.3-11.9)	19.18
ACTH (adrenocorticotropin) [pg/mL] (4.70-48.80)	39.23
Prolactin [ng/mL] (4.6-21.4)	17.37
IGF-1 (insulin-like growth factor) [ng/mL] (193-731)	263
GH (growth hormone) [ng/mL] (0-3)	5.08
TSH (thyroid-stimulating hormone) [µIU/mL] (0.51-4.3)	2.38
FT4 (free thyroxine) [ng/dL] (0.98-1.63)	1.27
Total calcium [mmol/L] (2.09-2.54)	2.61
Ionized calcium [mmol/L] (1.12-1.32)	1.39
Insulin [µIU/mL] (2.6-24.9)	11.3
C-peptide [ng/mL] (0.90-7.10)	1.08
Glucagon [ng/L] (<209)	140
Gastrin [pg/mL] (13-115)	<10.0
Chromogranin A [µg/L] (0-100)	45.62
Neuron-specific enolase [ng/mL] (0.00-16.30)	9.16
Glycated hemoglobin [%] (4.80-5.90)	5.14
Parathyroid hormone [pg/mL] (15.00-65.00)	46.97

Tab. 3. Results of laboratory test of a 14-year-old girl

Parameter	Value
Cortisol [µg/dL] (7 am - 10 am: 6.2-19.4; 4 pm – 8 pm: 2.3-11.9)	18.12
ACTH (adrenocorticotropin) [pg/mL] (4.70-48.80)	22.74
Prolactin [ng/mL] (6.0-29.9)	12.0
IGF-1 (insulin-like growth factor) [ng/mL] (183-850)	507
GH (growth hormone) [ng/mL] (0-3)	6.93
TSH (thyroid-stimulating hormone) [µIU/mL] (0.51-4.3)	1.2
FT4 (free thyroxine) [ng/dL] (0.98-1.63)	1.05
Total calcium [mmol/L] (2.09-2.54)	2.83
Ionized calcium [mmol/L] (1.12-1.32)	1.52
Insulin [µIU/mL] (2.6-24.9)	21.6
C-peptide [ng/mL] (0.90-7.10)	1.9
Glucagon [ng/L] (<209)	150
Gastrin [pg/mL] (13-115)	<10.0
Chromogranin A [µg/L] (0-100)	59.95
Neuron-specific enolase [ng/mL] (0.00-16.30)	3.09
Glycated hemoglobin [%] (4.80-5.90)	4.94
Parathyroid hormone [pg/mL] (15.00-65.00)	94.99

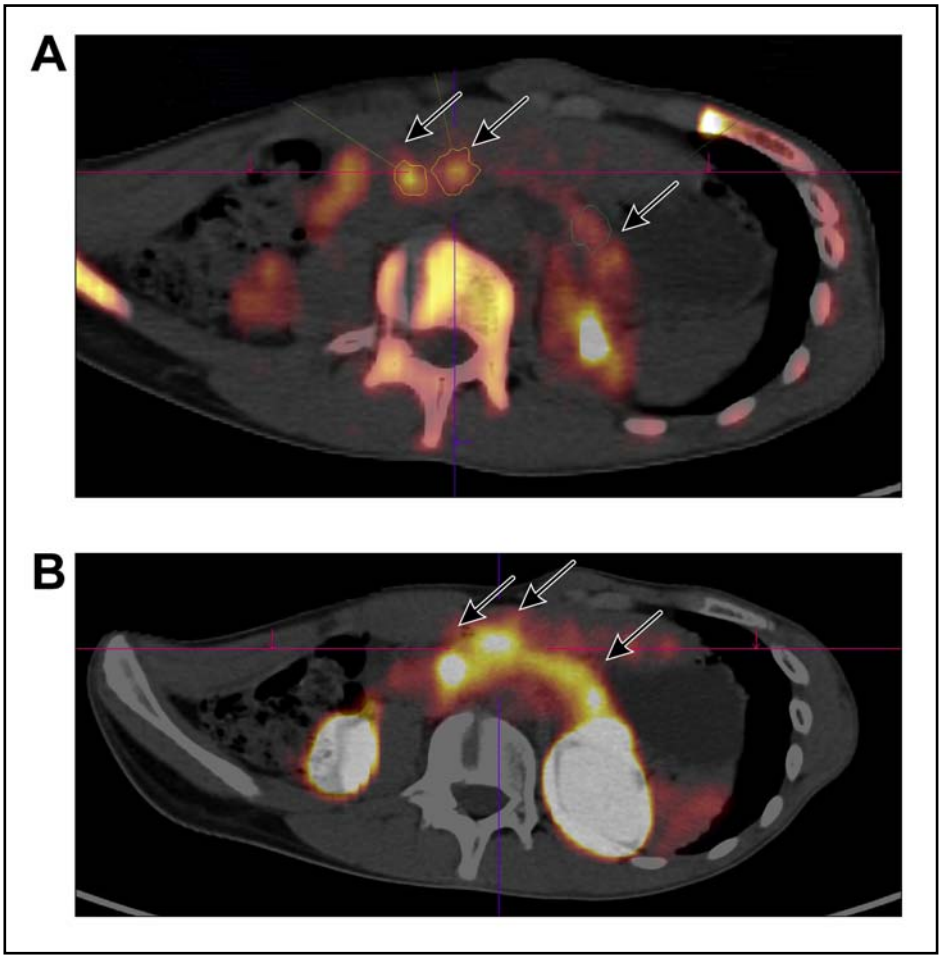

Fig. 2. PET (positron emission tomography) with various tracers from the boy diagnosed with MEN1 (multiple endocrine neoplasia type 1) syndrome. A: ^{18}F-DOPA PET-CT (fluorine-18-L-dihydroxyphenylalanine positron emission tomography-computed tomography scan), B: ^{68}Ga-GLP1 PET-CT (glucagon-like peptide-1 positron emission tomography-computed tomography scan). Arrows indicate the location of focal lesions in the pancreas. A marked difference in the intensity of DOPA metabolism and GLP1 storage is visible. SUV (standardized uptake value) of foci in the range of 2.0-5.0.

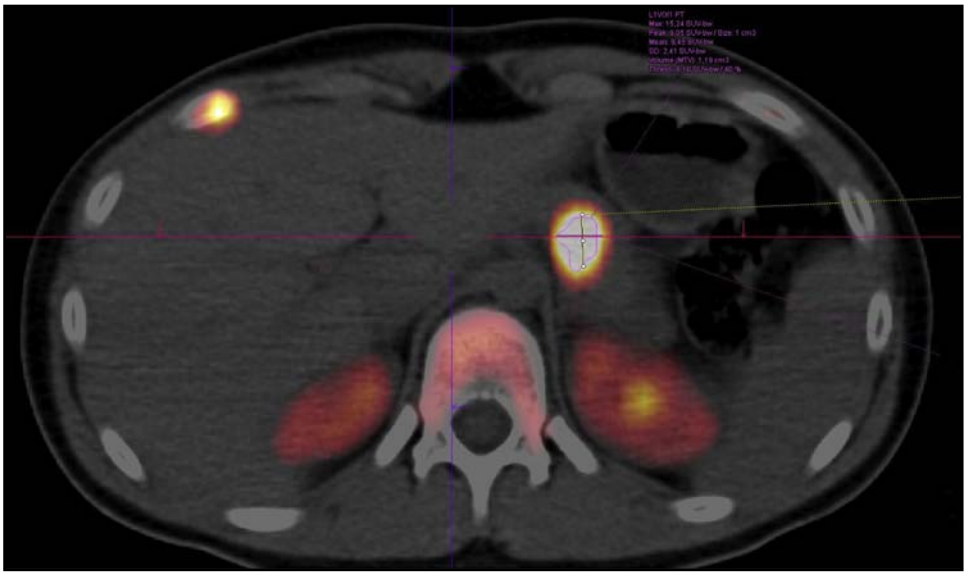

Fig. 3. PET (positron emission tomography): ^{18}F-DOPA PET-CT (fluorine-18-L-dihydroxyphenylalanine positron emission tomography-computed tomography scan) from the girl diagnosed with MEN1 (multiple endocrine neoplasia type 1) syndrome. A single focus of markedly increased tracer metabolism (SUV (standardized uptake value) 15.0) is visible in the tail of the pancreas.

treatment for hydrocephalus, the tumor was removed without complications. In the histopathological examination, the tumor corresponded to ganglioglioma GI. Moreover, the girl underwent subtotal parathyroidectomy, with a fragment of the right inferior parathyroid gland left in place. However, due to persisting hypercalcemia several months after the surgery, a reoperation was conducted to further reduce the fragment of the remaining parathyroid gland. Given the size of the pancreatic tumor and oncologic concern, and despite the lack of hormonal activity, the tumor was resected together with the tail of the pancreas. Histopathological examination revealed neuroendocrine tumor glucagonoma G1, pT1, N0 with a maximum dimension of 1.4 cm, and a Ki67 proliferative index below 3%.

The medical history of the patients' father was obtained from their mother and included kidney stone disease and acute pancreatitis. Two focal lesions, 10 mm in diameter and located in the body and tail of the pancreas, were visualized with upper gastrointestinal tract endoscopic ultrasonography. Cytological image analysis and immunohistochemical examination indicated neuroendocrine tumors. An ultrasonography revealed primary hyperparathyroidism (Table 4) with enlarged parathyroid glands, and MIBI scintigraphy showed a focus suggestive of adenoma within the right superior parathyroid gland. A CT of the abdominal cavity showed nodular alterations in the adrenal glands, and laboratory tests confirmed hypercortisolism.

A detailed family history obtained from the patients' father revealed that his brother had peptic ulcer disease, and his father died at the age of 48, most probably because of duodenal ulcer perforation.

The results of the *MEN1* gene analysis confirmed multiple endocrine neoplasia type 1 in the father, his daughter and son. A pathogenic c.1233_1234delinsT, p.(His412Thrfs*33) variant was detected in a single allele of the *MEN1* gene.

DISCUSSION

Most of the scientific literature concerning the MEN1 syndrome focuses on adult cases. It is estimated that the first symptoms of the disease appear before the age of 20 in approximately 43% of affected individuals, before 35 in 85% of individuals, and before 50 in 94% of individuals (Giusti *et al.* 2017; Giust *et al.* 2019). The most common clinical manifestation of MEN1, hyperparathyroidism resulting from parathyroid hyperplasia, is present in approximately 95% of cases (Thakker *et al.* 2012). Endocrine pancreatic tumors occur in 30-70% of cases, including insulinoma in 10% and endocrine-inactive tumors in 20-55% of cases. Pituitary gland tumors are recognized in 30-40% of individuals with MEN1 syndrome, with prolactinoma being the most common (20%) (Thakker, 1998). Among reports describing the MEN1 syndrome in children, mainly case studies are available. A French study involving a cohort of 160 patients younger than 21 described a 3-year-old patient whose symptoms were associated with an adrenal gland tumor (Gudet *et al.* 2015). The first symptoms included hyperparathyroidism in 75% of enrolled patients, pituitary gland adenoma in 34%, insulinoma in 12%, endocrine-inactive pancreatic tumor in 9%, gastrinoma in 2%, and malignant tumors of the adrenal gland and thymus in 1% of patients. In 14% of patients the first symptoms appeared before the age of 10, and in 3% before the age of 5 (Gudet *et al.* 2015). In the case study described here, the girl encountered the first symptoms when she was 7, and they were most probably associated with hyperparathyroidism. However, she was diagnosed at the age of 14 only because the clinical manifestation of the syndrome appeared in her brother. The boy demonstrated insulinoma symptoms when he was 12, and diagnosis was eventually made when he was 17. The father experienced the first symptoms associated with hyperparathyroidism in the third decade of life. In available case studies, most patients manifest one or two disorders typical of MEN1 in the first or second decade of life. Notably, the expression of MEN1 syndrome in the girl, described in this paper, was asymptomatic. She was diagnosed with primary hyperparathyroidism, a pancreatic tumor, lipomas of the sphenoid bone and petrous part of the temporal bone, and ganglioglioma located near the pineal gland and *lamina tecti*. To the best of our knowledge, there are no cases of ganglioglioma in this location reported for MEN1 syndrome (Griessenauer *et al.* 2014). In children, prolactinoma is the most common anterior pituitary gland tumor (Goudet *et al.* 2015; Vannuci *et al.* 2018; Vergès *et al.* 2002). It occurs so far more frequently in females. Up to date, only one case, that of a 5-year-old boy, has been described in children younger than 10 (Stratakis *et al.* 2000). Meningiomas are also observed in the central nervous system of individuals with MEN1 syndrome (8%) (Giust *et al.* 2019; Thakker, 1998; Thakker *et al.* 2012). Analyses of large cohorts of children with central nervous system ganglioglioma, published in 2014 and 2015, did not mention any cases of MEN1 syndrome (Griessenauer *et al.* 2014; Puget *et al.* 2015). The authors underlined the course of the disease complicated by hydrocephalus, which was also present in the

Tab. 4. Results of laboratory test of the patients' father

Parameter	Value
Cortisol [μg/dL] (7 am - 10 am: 6.2-19.4; 4 pm – 8 pm: 2.3-11.9)	15.69
ACTH (adrenocorticotropin) [pg/mL] (4.70-48.80)	20.73
Prolactin [ng/mL] (4.6-21.4)	19.56
IGF-1 (insulin-like growth factor) [ng/mL] (101-267)	203
GH (growth hormone) [ng/mL] (0-3)	3.51
TSH (thyroid-stimulating hormone) [μIU/mL] (0.51-4.3)	0.36
FT4 (free thyroxine) [ng/dL] (0.98-1.63)	0.9
Total calcium [mmol/L] (2.09-2.54)	2.99
Ionized calcium [mmol/L] (1.12-1.32)	1.58
Insulin [μIU/mL] (2.6-24.9)	15.4
C-peptide [ng/mL] (0.90-7.10)	3.74
Glucagon [ng/L] (<209)	-
Gastrin [pg/mL] (13-115)	66.9
Chromogranin [μg/L] (0-100)	48.94
Metanephrine in a 24-h urine collection (0.00-350.00)	46.06
Glycated hemoglobin [%] (4.80-5.90)	5.52
Parathyroid hormone [pg/mL] (15.00-65.00)	112.4
5-Hydroxyindoleacetic acid in a 24-h urine collection (2.00-6.00)	5.18

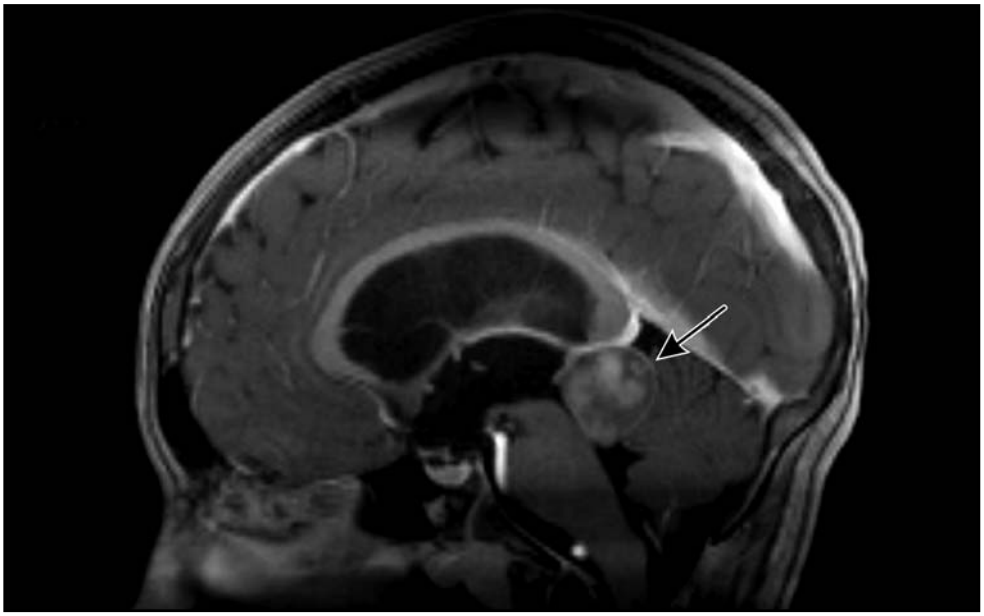

Fig. 4. The girl with MEN1 (multiple endocrine neoplasia type 1) syndrome – results of magnetic resonance imaging. The arrow indicates the central nervous system tumor located within the pineal gland and *lamina tecti*.

girl described here, and which required urgent surgery. Moro *et al.* attempted to connect glioma/ganglioglioma and pituitary gland adenomas in the course of MEN1 (Moro *et al.* 2004). They indicated the possibility of neuronal metaplasia of anterior pituitary gland cells.

The pancreas is the second most common location of lesions in MEN1 syndrome in adults and third in younger patients (Goudet *et al.* 2015; Vannucci *et al.* 2018). In the family described here, all individuals who carried the *MEN1* mutation were diagnosed with pancreatic lesions. The difficulties to diagnose the boy are worth underlining. The interpretation of the diagnostic fast test was not straightforward. Similar difficulty in the interpretation of this test has been reported by others (Guettier *et al.* 2013; Falconi *et al.* 2016). In the last few years, the insulin level thresholds in the diagnostic fast test were dropped. The first test was conducted when the boy was 13, and the result was interpreted as borderline according to the normal range valid at that time (Guettier *et al.* 2013). Many observations indicate the low sensitivity of medical imaging in the case of small tumors (<1 cm) (Gauger *et al.* 2003; Gonçalves *et al.* 2014; Howe *et al.* 2020). Below, we discuss the usage of EUS examination in pediatric patients. There are no recommendations regarding the patient's age when qualifying for EUS (Howe *et al.* 2020). According to valid recommendations from 2016, an endocrine-inactive pancreatic tumor with a size ≥ 2 cm is an indication for surgery (Falconi *et al.* 2016; Triponez *et al.* 2006; Triponez *et al.* 2006). However, no explicit recommendations are available for children (Gonçalves *et al.* 2014). Given possible complications and the risk associated with consecutive surgeries, decisions regarding the surgery should be cautious, and the smallest possible resections should be considered. Small, multifocal lesions can prove problematic because they do not allow for a typical resection. The case of the boy described here can serve as an example of the risk associated with conserving non-anatomical pancreatic resections (lesion expounding), which is preferred in children. Need for reoperation due to leaking in a location where a lesion was excised (between the head and body of the pancreas) demonstrated the risk associated with conservative surgeries of multifocal lesions. In this case, reoperation not only eliminated the complication resulting from the first surgery, but also allowed for more aggressive treatment. In the girl, given tumor size exceeding 2 cm and a lack of multifocality, it was decided to remove the lesion together with the tail of the pancreas. The postoperative period was, as in most typical pancreatic resections, uncomplicated. The histopathological examination revealed glucagonoma, although no typical clinical manifestation appeared.

The issues of right timing and the surgical technique for primary hyperparathyroidism remain controversial (De Menezes Montenegro *et al.* 2019; Marini *et al.* 2018). The application of criteria used for intermittent hyperparathyroidism is proposed in some papers. However, a long time of asymptomatic hyperparathyroidism, occurring in MEN1 syndrome, can affect bone mineral density (Tonelli *et al.* 2012). Normalization of the plasma calcium level allows to avoid renal complications and is beneficial in case of hypergastrinemia. Subtotal parathyroidectomy with a cervical remnant or total parathyroidectomy with possible autotransplantation of parathyroid tissue to the forearm are recommended (Thakker *et al.* 2012). In the course of parathyroidectomy in men, thymectomy should be considered, especially in smokers and in individuals with a family history of cancer. In the case of the family described here, both children underwent subtotal parathyroidectomy with approximately ½ of one parathyroid left in place. Reoperation with further reduction of parathyroid gland tissue was conducted due to persisting

hypercalcemia several months after the initial surgery. It was associated with difficulties assessing the activity of the parathyroid tissue that remained after the first surgery, an issue that is often described in the literature (Goudet *et al.* 2015; Keutgen *et al.* 2016).

In the 2012 guidelines (Goudet *et al.* 2015), no optimal strategy for choosing medical imaging is provided, and the minimum protocol suggests MRI, CT and EUS examination. The case of the family presented here demonstrates a limited usefulness of MRI and CT in the assessment of the pancreas, especially for small or multiple lesions. Ultrasonography can serve as a repeatable, noninvasive, and inexpensive alternative. However, PET with a tracer other than glucose analogue, fluorine-18 fluorodeoxyglucose (FDG), remains the gold standard of diagnostics. Typically, ^{18}F-DOPA PET-CT imaging is performed in neuroendocrine pancreatic tumors. It is characterized by high sensitivity and specificity, allowing for localizing even small lesions. In selected cases, like the boy described here, given different expression of membrane receptors, ^{68}Ga GLP1 PET-CT with a glucagon tracer can provide a higher sensitivity than ^{18}F-DOPA PET-CT imaging. The ongoing rapid development of conventional nuclear medicine and PET-CT imaging, together with broader availability of EUS examination, allows for early detection of even small lesions, which could not be visualized with other diagnostic techniques (Howe *et al.* 2020).

The analysis of families at risk of MEN1 syndrome, involved in the screening, and individuals with confirmed *MEN1* mutation, revealed that biochemical tests, in particular the determination of chromogranin A, pancreatic polypeptide, and glucagon levels, demonstrate limited sensitivity (De Laat *et al.* 2013; Qiao *et al.* 2014). A large diagnostic value is attributed to measurements of ionized calcium levels because increased concentration of parathyroid hormone is a late marker of hyperparathyroidism.

Genetic diagnostics play a crucial role in the evaluation of MEN1 syndrome (Pieterman *et al.* 2009). Individuals without the *MEN1* mutation do not need to be included in the screening. However, even if the MEN1 mutation is absent in a patient with clinical manifestation of MEN1 syndrome, it is recommended to perform observation and screening in his first-degree relatives. Moreover, according to the recommendations, it is necessary to conduct genetic analysis for MEN1 in every child who presents even one clinical manifestation involving the parathyroid glands, the pituitary gland, or the pancreas (Goudet *et al.* 2015).

The timing of surgeries, in particular for asymptomatic diagnoses in young individuals, remains an open issue (Newey *et al.* 2009). The goal of treatment is to reduce morbidity and mortality, but also to retain pancreatic function as long as possible and to avoid complications related to frequent surgeries.

Untreated individuals affected with MEN1 syndrome are characterized by reduced life expectancy, with a high probability of death before the age of 50. Approximately 2/3 of deaths due to MEN1 syndrome are associated with tumor malignancy (Goudet *et al.* 2010; Ito *et al.* 2013). Tumors in MEN1 are typically more difficult to operate. They are also usually multiple, metastatic, larger, more aggressive, and treatment-resistant. Highly malignant tumors are observed even in the youngest patients, like the report of a 3-year-old boy with an adrenal gland tumor (Goudet *et al.* 2010).

SUMMARY

The familial case reported here provides evidence of the diagnostic and therapeutic difficulties related to MEN1 syndrome. In the last few years, the number of suitable biochemical tests and imaging modalities has increased markedly. An immediate availability of genetic testing seems to be crucial to determine a diagnostic algorithm. In children, especially in the case of asymptomatic tumors, it is important to balance the benefits of an early surgery with the risk of possible surgical complications and the consequences of a loss of function of an endocrine gland.

DECLARATION OF INTEREST

All of the authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

All of the authors contributed equally to this work.

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