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MEN 2B syndrome – paediatric case report

Zespół MEN 2B pediatryczny – opis przypadku

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Abstract

Multiple endocrine neoplasia 2B (MEN 2B) is a rare syndrome caused by mutation of the *RET* proto-oncogene. Early-onset medullary thyroid carcinoma (MTC), marfanoid habitus, and mucosal neuromas occur in most cases, and some patients develop pheochromocytoma in later life. We present a case of a 16-year-old girl diagnosed with MEN 2B syndrome with an atypical course of the disease. Our patient had no family history of MTC and presented short stature instead of marfanoid features. Rare ophthalmological manifestations also occurred. The example of this patient proves that rare endocrinological syndromes should be taken into consideration when diagnosing unclear symptoms, even if not all of the typical manifestations are present.

Key words:

MEN 2B, multiple endocrine neoplasia, paediatric patient, short stature, medullary thyroid cancer.

Streszczenie

Zespół MEN 2B jest rzadko występującym zespołem, spowodowanym mutacją onkogenu *RET*. Wczesny rozwój raka rdzeniastego tarczycy (*medullary thyroid carcinoma* – MTC), marfanoidalna budowa i nerwiaki śluzówek występują w większości przypadków. U części pacjentów rozwija się pheochromocytoma w późniejszym okresie. W pracy przedstawiono przypadek 16-letniej pacjentki z rozpoznanym zespołem MEN 2B z nietypowymi objawami choroby. Pacjentka nie była obciążona rodzinnie rakiem rdzeniastym tarczycy, była niskiego wzrostu w miejsce marfanoidalnego wyglądu. Występowały rzadkie objawy oczne. Przykład tej pacjentki dowodzi, że przy diagnozowaniu niejasnych objawów należy wziąć pod uwagę rzadkie zespoły endokrynologiczne, nawet jeśli nie występują wszystkie typowe objawy.

Słowa kluczowe:

dzieci, niski wzrost, MEN 2B, zespół wielogruczolakowatości, rak rdzeniasty tarczycy.

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Introduction

A tendency for some endocrine neoplasms to occur simultaneously with other endocrinological tumours was first observed in the beginning of the 20th century. In 1968 Steiner *et al.* firstly referred to this as "multiple endocrine neoplasia" (MEN) [1]. Currently, MEN is being described as an autosomal dominant, multisystemic disease with high penetrance, featuring tumours of endocrine glands. Three syndromes are distinguished within the disease (Table 1): MEN 1 – Wermer syndrome and MEN 2, further divided into MEN 2A – Sipple syndrome and MEN 2B – Wagenmann-Froboese syndrome [2, 3]. Clinically, MEN 1 and MEN 2 differ in the frequency of medullary thyroid carcinoma (MTC) incidence and the malignancy rate; in most cases, MEN 1 neoplasms are benign in contrast to malignant in MEN 2 [4].

MEN 1 manifests in parathyroid (90% of cases), pancreatic (half of the cases), and pituitary gland tumours [5]. Occasionally, adenomas of thyroid and adrenal glands occur as well. Genetically it is mostly caused by the mutation in the *MEN1* gene, which encodes menin. Characteristics of the patients include elevated levels of insulin, gastrin, and other gastrointestinal tract related hormones [6]. Abnormally high gastrin concentration stimulates the gastric acid secretion and hence often gastric ulcers and gastrointestinal tract mucosa irritation. Pituitary gland tumours mostly secrete prolactin and growth hormone [7]. Due to the parathyroid hyperplasia, hypercalcaemia also occurs.

MEN 2 development is most commonly connected with M918T mutation of *RET* proto-oncogene, which encodes the TGF-β receptor [8]. Mutation may be inherited in an autosomal dominant way or occur simultaneously (*de novo*) [9]. Diagnosis of MEN 2 syndrome includes DNA testing and calcitonin level assessment as a supporting preliminary test [10]. Among patients with *RET* gene mutations, prophylactic thyroidectomy is performed before the age of one year to avoid future complications [11,12].

MEN 2A syndrome is characterised by higher occurrence of medullary thyroid carcinoma [13]. In comparison to MEN 2B, not all the cases are malignant, 14% of patients present benign C-cell hyperplasia [14]. Another two commonly coexisting diseases are pheochromocytoma (40% of cases) and hyperparathyroidism (35% of cases) [15].

MEN 2B manifests with aggressive medullary thyroid cancer among all patients (100%) [13]. Half of them are also affected by pheochromocytoma. As well as malignant tumours, benign lesions also develop, i.e. in the submucosa, eyes, and mouth [3]. Young patients have a very characteristic marfanoid appearance with low muscle mass, irregular masses beneath mucosal surfaces, and dry eyes due to the almost total lack of tears [16]. The symptoms often include yellowish, painless nodules in the oral cavity. Neuromas are in fact nervous masses composed of hyperplastic Schwann cells [17].

Case report

A 16-year-old female patient with no family history of thyroid cancer had been under the care of an endocrinologist since early childhood due to short stature and hypothyroidism. A family tree including three generations was created, indicating that the patient has a family history for Graves' disease (patient's mother, now asymptomatic) and nodular goitre (paternal aunt and paternal grandfather). Two other paternal family members also underwent thyroid surgery for unknown reasons. The patient was born at term, with an Apgar score of 9 at one minute, birth weight 3600 g, and birth length 55 cm. Her medical history was significant for glaucoma diagnosed at the age of eight months. From the age of three, the patient's height remained below third percentile with weight within normal range (between the 25th and 50th percentile. Thorough diagnostics was performed at patient's age of four years to find the cause of her short stature. Bone age assessment revealed delayed skeletal age. Nocturnal growth hormone levels were below normal ranges (all the values were less than 10 ng/ml with a peak of 5.58 ng/ml at 150 minutes). Growth hormone glucagon stimulation test results were within normal ranges (peak at 20.4 ng/ml), which allowed initial exclusion of growth hormone deficiency. Turner's syndrome and celiac disease were also excluded. Genetic counselling revealed subtle dysmorphic features, such as broad nasal tip, high-arched palate, and abnormalities of the oral cavity mucosa in the form of tongue fibroids and

Table I. MEN1 and MEN2 differences

	MEN 1	MEN 2	
Type	–	A	B
Mutated genes	*MEN1* (11q13)	*RET* (10q11.2)	
Common disorders	parathyroid hyperplasia, pancreatic and pituitary gland tumours	medullary thyroid carcinoma, pheochromocytoma	mucosal neuroma, medullary thyroid carcinoma, pheochromocytoma

macroglossia. Further tests indicated partial primary deficiency of insulin-like growth factor (IGF-1) as the underlying cause of the patient's short stature.

As mentioned above, the had also been suffering from hypothyroidism since early childhood. Thyroid peroxidase (TPO) antibodies were negative. She had been treated with modified levothyroxine doses in order to be kept in euthyreosis until the age of 12 years when hyperthyroidism occurred – thyroid stimulating hormone (TSH) $<$ 0.005 mU/ml (0.4–4.0), free thyroxine (free T4) 23.18 pmol/l (10–22), free triiodothyronine (free T3) 8.54 pmol/l (4–6.8). Due to hypothyroidism, ultrasound examination of the thyroid gland was routinely performed every 6 to 12 months. At the patient's age of 12 years, ultrasonography imaging revealed two small, well-defined hypoechoic structures without significantly visible vascularisation in both right and left lobe, the first with dimensions of 8.4 $\times$ 5.7 $\times$ 6.6 mm and the second measuring 17 $\times$ 8.3 $\times$ 9 mm. Due to their significant progression in size over nine months a fine-needle aspiration cytology (FNAC) was performed for malignancy risk stratification (patient's age 14 years). At the time, thyroid hormone levels were stabilised with TSH 1.77 mU/ml, free T4 1.18 pmol/l, and free T3 3.48 pmol/l.

Both examined nodules were classified as suspicious for malignancy – Bethesda category V using the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). There is an overall 60–75% risk of malignancy in this category, indicating surgical lobectomy or near-total thyroidectomy as the recommended clinical management. In line with the recommendations, the patient was referred to a paediatric surgical ward for further treatment. Although papillary thyroid carcinoma was the preliminary diagnosis due to the fine-needle biopsy result, the clinical suspicion was medullary thyroid carcinoma (MTC) connected with MEN 2B syndrome.

On admission to the surgery department the thyroid ultrasound examination was repeated. It revealed a steady increase in nodule size, with dimension 19 $\times$ 10 $\times$ 10 mm in the right lobe and 26 $\times$ 15 $\times$ 12 mm in the left lobe. Lesions were characterised by heterogeneous, hypoechoic structure, the presence of microcalcifications, and increased blood flow pattern. Physical examination revealed lymphadenopathy in submandibular and axillary areas (lymph nodes up to 14 mm and 12 mm, respectively) as well as enlargement of cervical and single inguinal lymph nodes (7 mm, 5 mm). No abnormalities were discovered on an ultrasound of the abdominal cavity. Serum carcinoembryonic antigen (CEA) was increased at 27.2 ng/ml, with reference level less than 5.0 ng/ml for non-smokers.

Due to the biopsy result the patient was immediately qualified for total thyroidectomy with intraoperative recurrent laryngeal nerve monitoring, thymectomy, and extended lymphadenectomy. Intraoperative histopathological examination of the left thyroid lobe showed poorly differentiated thyroid carcinoma, indicating that in accordance with clinical data medullary thyroid carcinoma (MTC) should be taken into consideration in differential diagnosis. No neoplastic cells were found in the parathyroid gland. A small metastatic focus was revealed in one of the left thyroid lymph nodes. The surgery was complicated by postoperative acute respiratory failure and hypocalcaemia, later stabilised in the intensive care unit. Perioperative basal calcitonin serum level reached 1042 pg/ml with a reference level of less than 11.5 pg/ml, initially confirming medullary thyroid carcinoma diagnosis.

Postoperative histopathological examination confirmed the diagnosis of multifocal medullary thyroid carcinoma. Left lobe tumour had a diameter of 15 mm and was non-encapsulated. Thyroid capsular invasion without penetration was present in the left lobe. The right lobe tumour had a diameter of 12 mm, was partially encapsulated, and limited to the tissue of origin. No vascular invasion was found, and the surgical margins were clear. Chronic lymphocytic thyroiditis and nodular goitre were found in the remnants of the thyroid tissue. Metastatic MTC microfoci (diameter $<$ 1 mm) and foci (diameter between 2 and 4 mm) were confirmed in four of dissected cervical lymph nodes on histopathological examination. Immunohistochemical expression of MTC markers calcitonin and amyloid were positive, and expression of thyroid transcription factor 1 (TTF-1) was weakly positive. Parathyroid gland and thymus tissue were described as normal.

Calcitonin serum level test was repeated two weeks after thyroidectomy and showed a decrease to 49.2 pg/ml. Postoperative serum calcium and ionised calcium levels were within normal ranges. According to elevated TSH level (15.86 mIU/ml) the thyroxine dose was increased from 75 μg to 100 μg per day. The patient was also receiving Alfadiol due to hypoparathyroidism. Laboratory tests performed three months after surgery revealed an increased level of phosphorus (5.4 mg/dl with normal range 2.8–5.0 mg/dl) and no other abnormalities.

The patient was subsequently screened for the *RET* protooncogene mutation. A pMet918Thr mutation in exon 16 (codon 918, c.2753 T$>$C, ATG$>$ACG, Met$>$Thr) was identified, confirming MEN 2B syndrome diagnosis. With regard to the specificity of the syndrome and its possible subsequent manifestations, the patient requires further observation and great vigilance. The patient remains under the control of an endocrinologist.

In order to exclude the presence of pheochromocytoma in adrenal glands, which is also characteristic for mutations in the *RET* gene, abdominal computed tomography imaging was performed. No abnormalities were detected. 24-hour urine sample for the presence of adrenaline metabolites showed a high concentration of methoxyadrenaline (62.05 μg/24 h with reference level under 33.3 μg/24 h for women) with methoxynoradrenaline and 3-methoxytyramine within normal range.

Since thyroidectomy the patient has remained under systematic endocrinological care, which includes monitoring biochemical parameters of the thyroid gland (PTH, TSH, free T4, calcium, ionised calcium, phosphorus) and adjusting thyroxine and Alfadiol doses according to the results. A recent examination showed symptomatic thyroid dysfunction (TSH 8.0 mU/ml) with dry skin in physical examination and weight gain of 5 kg over two months. The patient complains of increased fatigue. Further endocrinological supervision and strong vigilance are required because the patient is at high risk of developing other malignant lesions.

Discussion

We presented a rare case of an atypical MEN 2B syndrome course in a paediatric patient. MEN 2B is a rare syndrome with prevalence estimated at approximately 0.2 per 100,000; it is especially uncommon in paediatric patients [18]. The Met918Thr mutation in exon 16 is the most common variant, being responsible for around 95% of MEN 2B cases, which was also the case in the described patient [19]. MEN 2B syndrome presents classically with medullary thyroid cancer (MTC), marfanoid body habitus, and oral cavity mucosal neuromas in all patients, with about 50% of patients developing pheochromocytoma (PC) [20]. Ophthalmic abnormalities, including mucosal neuromas of conjunctiva, dry eyes or glaucoma, motor and muscle deficiencies, severe constipation, and ganglioneuromas of the intestinal tract may also be found in MEN 2B patients. Extra-endocrine features tend to manifest far earlier than the age at which endocrine signs become apparent [21, 22]. Glaucoma has been reported in both adult and paediatric patients; however, it is not as common as mucosal lesions [23, 24]. Due to this clinical picture, MEN 2B may be suspected early in childhood mostly by the presence of marfanoid phenotype and mucosal neuromas and fibroids on the dorsal surface of the tongue, palate, or pharynx [3, 25].

Although the patient presented oral cavity fibroids and glaucoma identified at a very young age, her short stature disturbed the typical marfanoid habitus. Those symptoms combined did not indicate MEN 2B syndrome as the most probable diagnosis in early childhood. By virtue of varied qualities, the patient could present some diagnostic difficulties. Nevertheless, due to the growth deficit and hypothyroidism, the patient remained under regular endocrine care. Ultrasound examination of the thyroid gland, performed regularly on account of thyroid gland insufficiency, allowed the detection of suspicious lesions at an early stage and introduction appropriate therapy (total thyroidectomy, thymectomy, and extended lymphadenectomy) and further diagnostics in time.

MEN 2B is characterised by the development of aggressive, early-onset MTC that typically presents in the first and second decade [21]. At the time of diagnosis, the patient was 14 years old, which corresponds with the mean age of MTC appearance. This type of carcinoma rarely occurs in paediatric patients; therefore, according to obligatory directives she was screened for the *RET* proto-oncogene mutation [26]. *De novo* pathogenic variant occurs with a probability of 5% or less in MEN 2A cases and 50% of MEN 2B cases [27]. The family medical history eliminated prevalence of MTC among first-degree relatives, excluding the fMTC diagnosis. Based on the Met918Thr mutation found in genetic testing, MEN 2B diagnosis could be made [27].

Despite the decreased postoperative MTC marker, the patient requires lifelong endocrinological care and oncological vigilance because thyroid cancer is usually the initial endocrinological manifestation of the syndrome, prognosticating pheochromocytoma, which develops in about 50% of MEN 2B patients at an older age [20, 28]. Due to slightly elevated methoxyadrenaline concentration in 24-hour urine sample, widened diagnostics of pheochromocytoma should be performed [29].

Conclusions

MEN 2B syndrome is a rare diagnosis in paediatric patients. Combined with her short stature, the described case may be considered a great rarity and proves that an atypical course of rare diseases has to be taken into consideration when diagnosing complex and unclear symptoms. Lack of typical manifestations may be very misleading and delay the proper diagnosis, especially when it is an uncommon one itself. General recommendations indicate that every histopathologically confirmed medullary thyroid carcinoma in paediatric patients requires further molecular diagnostics and genetic screening for *RET* gene mutations that may cause MEN 2B syndrome. Diagnosis of MEN 2B demands genetic screening of the patient's first-degree relatives. Due to increased incidence of pheochromocytoma in later life, MEN 2B patients have to remain under long-term endocrinological care and require increased oncological vigilance.

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