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Catecholamine crisis as a first manifestation of familial bilateral pheochromocytoma caused by RET proto-oncogene mutation in codon C 634R

Przełom katecholaminowy jako pierwsza manifestacja rodzinnego obustronnego guza chromochłonnego w przebiegu mutacji protoonkogenu RET w kodonie C 634R

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Abstract

Introduction: Multiple endocrine neoplasia type 2 (MEN 2) is a genetic disorder caused by mutation in the RET proto-oncogene. MEN 2A includes medullary carcinoma of the thyroid, pheochromocytoma, and primary hyperparathyroidism. The authors present a case study of three family members with bilateral pheochromocytoma in the course of MEN 2A, a catecholamine crisis being the first manifestation of the syndrome in one of them.

Case 1: A 30-year-old man without a history of hypertension or any other chronic medical problems was admitted to the Emergency Department because of a hypertensive crisis that was followed by cardiac arrest. A later diagnosis revealed bilateral pheochromocytoma and RET proto-oncogene mutation in codon 634. The patient underwent bilateral adrenalectomy and total thyroidectomy; the latter confirmed the presence of medullary carcinoma.

Case 2: The patient underwent right adrenalectomy with the removal of a pheochromocytoma at the age of sixteen. Ten years later, a suspicion of pheochromocytoma in the remaining left adrenal was raised. Mutation in the RET proto-oncogene was confirmed as well. The patient first underwent left adrenalectomy and then she had total thyroidectomy. Postoperative histopathological examinations revealed pheochromocytoma and medullary carcinoma.

Case 3: Radiological and biochemical examination confirmed pheochromocytoma. Therefore, the two adrenals were removed. As mutation in codon 634 was detected, the patient underwent total thyroidectomy as well. The presence of medullary carcinoma was confirmed.

Conclusions: Pheochromocytoma is a rare and potentially lethal disease if a catecholamine crisis develops. Its recognition requires further investigation towards genetic syndromes, particularly MEN 2A. **(Endokrynol Pol 2015; 66 (5): 462–468)**

Key words: *multiple endocrine neoplasia type 2A; hypertensive crisis; pheochromocytoma*

Streszczenie

Wstęp: Zespół mnogich nowotworów gruczołów dokrewnych typu 2 (MEN 2, *multiple endocrine neoplasia type 2*) jest dziedzicznym zespołem spowodowanym mutacją protoonkkogenu RET. Do MEN 2 zalicza się zespoły: MEN 2A, MEN 2B oraz rodzinnego raka rdzeniastego tarczycy (FMTC, *familial medullary thyroid carcinoma*). W skład zespołu MEN 2A wchodzą: rak rdzeniasty tarczycy, guz chromochłonny oraz pierwotna nadczynność przytarczyc. Autorzy przedstawiają historię 3 członków rodziny z obustronnym guzem chromochłonnym w przebiegu MEN 2A oraz przełom katecholaminowy będący pierwszą manifestację zespołu u jednego z nich.

Przypadek 1: 30-letni mężczyzna dotychczas zdrowy, zgłosił się do Szpitalnego Oddziału Ratunkowego z powodu przełomu nadciśnieniowego, po którym doszło do zatrzymania krążenia. Przeprowadzona diagnostyka ujawniła obustronny guz chromochłonny oraz mutację protoonkogenu RET w kodonie 634. Pacjenta poddano obustronnej adrenalektomii oraz całkowitej tyreidektomii. Pooperacyjne badanie histopatologiczne tarczycy potwierdziło ogniska raka rdzeniastego.

Przypadek 2: Chora przeszła prawostronną adrenalektomię z powodu pheochromocytoma. Dziesięć lat później wysunięto podejrzenie pheo w pozostałym nadnerczu. Stwierdzono mutację protoonkogenu RET. Chorą poddano lewostronnej adrenalektomii, a następnie całkowitej tyreidektomii. Pooperacyjne badania histopatologiczne potwierdziły wstępne podejrzenia pheo i raka rdzeniastego.

Przypadek 3: Zarówno badania obrazowe, jak i badania laboratoryjne budziły podejrzenie pheochromocytoma. W związku z tym, dwa nadnercza usunięto. Badanie histopatologiczne potwierdziło wstępne rozpoznanie. Po stwierdzeniu mutacji w kodonie 634 pacjent przeszedł ponadto całkowitą tyreidektomię. Stwierdzono ogniska raka rdzeniastego w materiale pooperacyjnym.

Wnioski: Pheochromocytoma jest rzadką, a ponadto potencjalnie śmiertelną chorobą, gdy wystąpi przełom katecholaminowy. Rozpoznanie pheochromocytoma nakazuje dalszą diagnostykę w kierunku zespołów genetycznych, w tym MEN 2A.

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Słowa kluczowe: *zespół mnogich nowotworów gruczołów dokrewnych typu 2; przełom nadciśnieniowy; guz chromochłonny*

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Introduction

Multiple endocrine neoplasia type 2 (MEN 2) is a multi-glandular autosomal dominant genetic disorder caused by mutation in the RET proto-oncogene. It is subdivided into MEN 2A, MEN 2B, and familial medullary thyroid carcinoma (FMTC). Typically, MEN 2A includes medullary carcinoma of the thyroid, pheochromocytoma, and primary hyperparathyroidism (PHP). In MEN 2B, similarly to MEN 2A, medullary carcinoma of the thyroid and pheochromocytoma are present. Additionally, MEN 2B includes neurofibromatosis and other congenital malformations. FMTC is recognised when at least two family members are affected by medullary carcinoma of the thyroid in the absence of pheochromocytoma or primary hyperparathyroidism [1, 2].

Multiple endocrine neoplasia type 2A is the most common of the three sub-types of MEN2. Yet, it is a rare syndrome; in the USA it affects 1/30,000–50,000 people [3, 4]. In Poland, 50–100 new cases of MEN 2A can be expected annually [5, 6]. Medullary carcinoma of the thyroid is the most common and usually the first manifestation of MEN2A. It is detected in 98% of RET proto-oncogene mutation carriers. Pheochromocytoma and primary hyperparathyroidism are less common presentations of MEN 2A. However, the clinical presentation of this syndrome is dependent on the particular codon mutation and can vary [2, 7–9].

The authors present a case study of three family members with bilateral pheochromocytoma in the course of MEN 2A, a catecholamine crisis being the first manifestation of the syndrome in one of them.

Case 1. M.K. (son), age at the moment of pheochromocytoma and MEN 2A recognition: 30 years

A 30-year-old man without a history of hypertension or any other chronic medical problems was admitted to the Emergency Department with severe abdominal pain, vomiting, nausea, fever, and dyspnoea. On admission, he had high blood pressure and tachycardia. Within a few hours cardiac and respiratory failure developed, followed by sudden cardiac arrest in the mechanism of asystole. Resuscitation was conducted effectively, yet the patient remained unconscious, demanding intubation and mechanical ventilation for a few days. The clinical picture of catecholamine crisis (high temperature, high labile values of blood pressure, supraventricular arrhythmias, cardiomyopathy) was confirmed by imaging studies — computer tomography revealed bilateral huge adrenal tumours: 88 × 73 mm in the left adrenal and 27 × 15 mm in the right adrenal, with typical radiologic features of pheochromocytoma (heterogeneous, irregular masses with areas of necrosis and calcification). The MR images raised suspicion of pheochromocytoma as well (Fig. 1, 2). Hormonal tests confirmed the initial diagnosis (elevated 24-hour urine collection of metanephrine, elevated plasma metanephrine and chromogranin A, as shown in Table I). The patient underwent laparoscopic right adrenalectomy and classic left adrenalectomy. Histopathological examination revealed a bilateral adrenal pheochromocytoma that stained positive for chromogranin and synaptophysin with Ki-67 index < 2%. After the mutation in the RET proto-oncogene was confirmed, the patient underwent total thyroidectomy. A postoperative histopathological

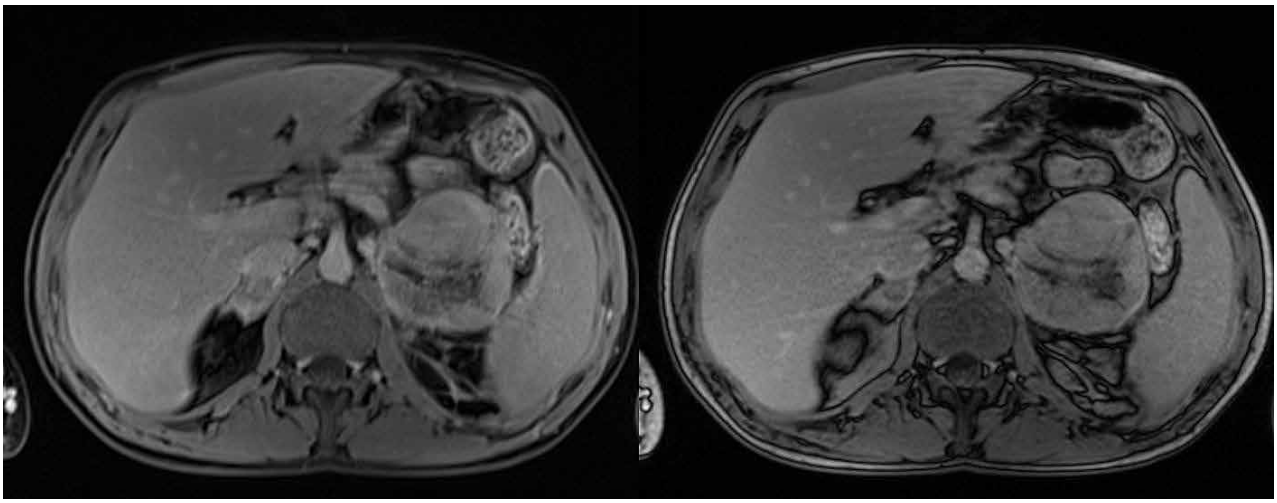

Figure 1. *Abdominal MR of patient MK. Heterogeneous nodular mass lesion in left adrenal gland (83 × 73 mm) on T1 on-phase and on T1 out-of-phase. Analogous lesion (26 × 57 × 34 mm) with areas of necrosis in right adrenal gland*

Rycina 1. *MR jamy brzusznej pacjenta MK. Heterogenna guzowata zmiana w lewym nadnerczu (83 × 73 mm) — obraz T1-zależny w fazie i przeciwfazie. Analogiczna zmiana (26 × 57 × 34 mm) z ogniskami martwicy w prawym nadnerczu*

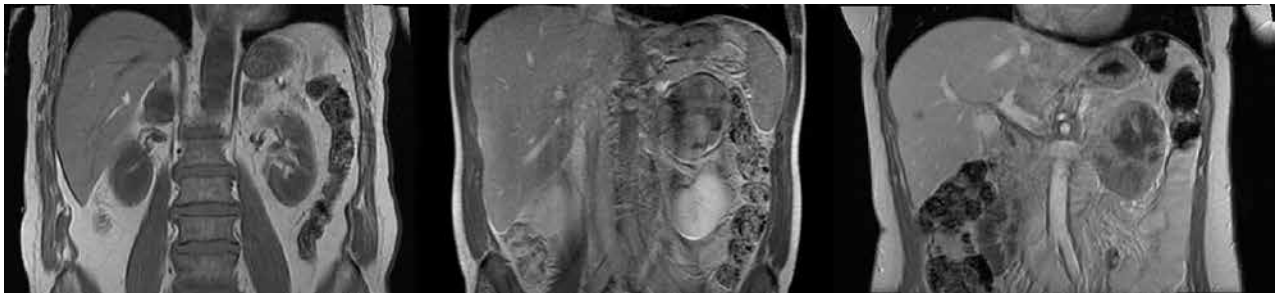

Figure 2. *Coronal magnetic resonance images of phaeochromocytomas in JK, MK, and PK (starting from the left)*
Rycina 2. *MR — projekcje czołowe guzów chromochłonnych u JK, MK, PK*

study revealed multiple foci of medullary carcinoma. The concomitance of primary hyperparathyroidism has been ruled out so far (due to a normal level of parathormone and calcium in the plasma).

Case 2. P.K. (daughter), age at the moment of pheochromocytoma recognition: 16 years; age at the moment of MEN 2A recognition: 28 years

P.K. is the family member in whom pheochromocytoma was detected first. So far she is also the youngest person in the family in whom the tumour has been diagnosed — right adrenalectomy with pheochromocytoma resection was performed in the year 2001 when the patient was sixteen. Yet, at that moment she has was not been screened for germline mutations. From 2003 until 2013 she did not stay under medical supervision. In the meantime, from 2006 episodes of tachycardia and rises in blood pressure were observed. An MR performed in February 2013 revealed a pathologic mass with radiological features in the remaining left adrenal gland raising suspicion of pheochromocytoma (Fig. 2, 3). Furthermore, the MR presented focal lesions in the liver suspected of metastases. Meanwhile, a 24-hour urine analysis detected elevated excretion of metanephrine (Table I). These findings were followed by left adrenalectomy, which confirmed the initial suspicion of pheochromocytoma in the remaining adrenal. In order to diagnose the focal lesions in the liver, iodine-123-meta-iodobenzylguanidine (MIBG) scanning and somatostatin scintigraphy were performed. However, these examinations did not give an answer as to the nature of the lesions. In September 2013 a control MR was performed. The examination did not show a progression of the hepatic lesions and, after performing a liver biopsy, focal nodular hyperplasia (FHN) was diagnosed. In February 2014, after the mutation in the RET proto-oncogene was confirmed, the patient underwent total thyroidectomy. A postoperative histopathological study revealed multiple foci of medullary carcinoma. Similarly to M.K., PHP has not been revealed so far.

Case 3. J.K. (father) age at the moment of MEN 2A recognition: 59 years

Bilateral masses in the adrenals were detected in 2008 in computed tomography. Since the tumours raised suspicion of malignancy (atrophic changes, low 10-minute delayed adrenal enhancement washout of contrast in computer tomography), the patient was qualified for adrenalectomy at that time. However, because of an unfavourable localisation of the tumours in relation to renal arteries, he was dismissed from the surgery. In the course of the irregular diagnostic process that followed (it started in 2010 and finished in 2013), an elevated level of metanephrine in 24-hour urine collection (Table I) was stated, and the MR and MIBG images were typical for pheochromocytoma (Fig. 2, 4). Adding to this the coexisting hypertension and positive history of pheochromocytoma in his children, an initial diagnosis of bilateral pheochromocytoma was made. In May 2013 the patient underwent bilateral adrenalectomy. Histopathological examination proved bilateral pheochromocytoma. In January 2014, when the presence of the mutation in the RET proto-oncogene in exon 11 p.C634R in the patient was confirmed, he underwent total thyroidectomy. Medullary carcinoma foci were found in the postoperative histopathological examination. The presence of PHP was ruled out at that time.

A rigorous medical history of the family revealed two additional deaths: J.K.'s mother (A.K) died during labour and her sister (U.M) died during pregnancy, which may be taken as confirmation of the diagnosis (Fig. 5). Furthermore, at the time, RET proto-oncogene mutation in exon 11 p.C634R was validated in two of the three remaining daughters (E.K. and E.S) of J.K. Two sons of M.K. at the age of 9 (J.K.) and 12 (R.K.) years are waiting for gene mapping.

Discussion

The presented family members all exhibit MEN 2A. They meet the clinical criteria of the syndrome as each of them has two out of three pathologies typical for

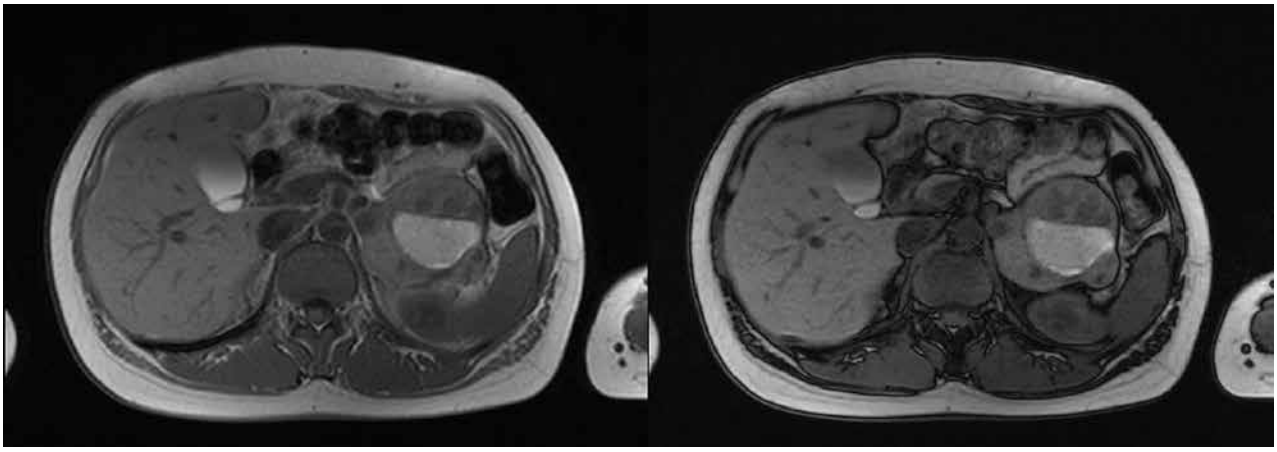

Figure 3. *Abdominal MR of patient PK. Large heterogeneous nodular mass lesion (100 mm × 75 mm × 80 mm) with areas of necrosis and haemorrhage in left adrenal gland on T1 on-phase and on T1 out-of-phase*

Rycina 3. *MR jamy brzusznej pacjentki PK. Duża heterogenna guzowata zmiana (100 × 75 × 80 mm) z ogniskami martwicy i wylewów w lewym nadnerczu — obraz T1-zależny w fazie i przeciwfazie*

Table I. *Clinical and laboratory characteristics of the K. family*

Tabela I. *Dane kliniczne i laboratoryjne rodziny K*

Patient		**MK**	**PK**	**JK**
Symptoms		Catecholamine crisis	Hypertension, palpitations, tachycardia	Hypertension, palpitations
Metanephrine	Before treatment	4.2	3.08	2.5
Urine mg/d	After treatment	< 0.35	< 0.6	< 0.25
(N < 1.0)				
Calcitonin	Before treatment	212	79	249
Plasma pg/mL	After treatment	< 18.2	< 2.0	< 3.2
(N < 18.2)				
Chromogranin A	Before treatment	2326	1155	165
Plasma ug/L	After treatment	34	64	23
(N: 19–98)				

MEN 2A. Furthermore, the genetic tests performed in the three patients, unambiguously confirm MEN 2A regardless of the classic clinical manifestation of the syndrome [2, 4]. The mutation in codon 634 is the most common and may concern 85% of all MEN 2A carriers [10].

Pheochromocytoma is a typical manifestation of MEN 2A. It is estimated that 30–50% of people affected by this syndrome have pheochromocytoma that is usually bilateral or multifocal [11, 12]. Meanwhile, pheochromocytoma as a first manifestation of MEN 2A occurs in 9–27% of cases [11, 13]. Mutation in codon 634 particularly predisposes to this tumour [11, 14]. At the same time, pheochromocytoma related to the mutation in codon 634 is very likely to develop in young age, even in children less than ten years old [15]. The described family members had bilateral pheochromocytoma, as is typical for this mutation. In P.K. the tumour was detected at a relatively young age — she was sixteen at that time. Furthermore, all of them presented classic manifestations of pheochromocytoma, including persistent hypertension (J.K.); blood pressure fluctuations and arrhythmias (P.K.) and even catecholamine crisis, the latter being the first manifestation of pheochromocytoma in M.K. Interestingly, pheochromocytoma related to MEN 2A can be asymptomatic. In a study of 46 cases of pheochromocytoma, Pomares et al. compared isolated

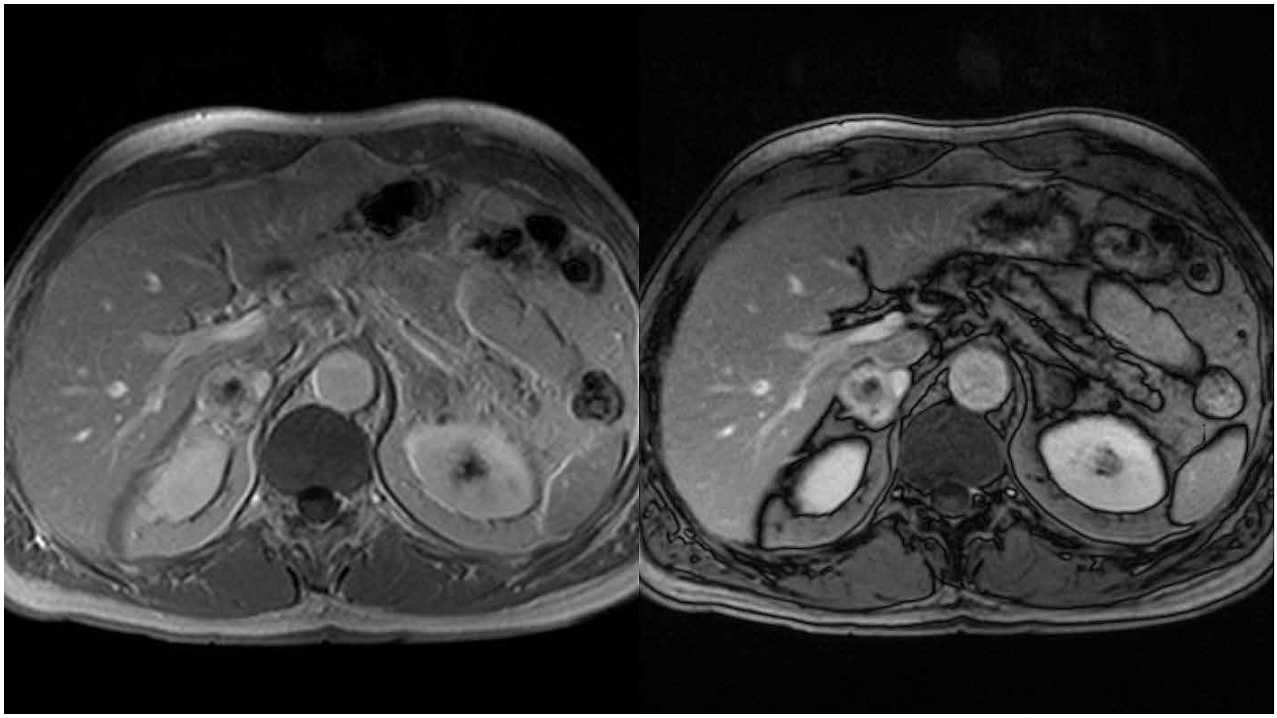

Figure 4. *Abdominal MR of patient JK. A well-defined heterogeneous nodular lesion in right adrenal gland (36 × 34 × 35 mm) with features of necrosis on T1 on-phase and on T1 out-of-phase. Analogous lesion (19 × 19 × 21 mm) in left adrenal gland*

Rycina 4. *MR jamy brzusznej pacjenta JK. Dobrze odgraniczona heterogenna guzowata zmiana w prawym nadnerczu (36 × 34 × 35 mm) z ogniskami martwicy — obraz T1-zależny w fazie i przeciwfazie. Analogiczna zmiana (19 × 19 × 21 mm) w lewym nadnerczu*

(23 cases) vs. familial pheochromocytoma (23 cases). In their study, from all the MEN 2A phaeochromocytomas 52% were asymptomatic, with only 35% presenting elevated blood pressure values. Instead, the majority of patients with isolated pheochromocytoma were symptomatic, having hypertension [15]. In the general population pheochromocytoma is a very rare cause of hypertension; its prevalence in patients with hypertension varies from 0.2 to 0.6% [16–20] and 4–6% of adrenal incidentalomas eventually turn out to be phaeochromocytomas [18, 21, 22]. Meanwhile, up to 30% of phaeochromocytomas have a genetic background [1, 19], mainly as part of MEN 2A, but also in von Hippel Lindau (VHL) syndrome, in the succinate dehydrogenase (SDH) gene family, or in neurofibromatosis type 1 (NF1). Therefore, the recognition of pheochromocytoma requires reviewing the patient's family history for cases of pheochromocytoma among relatives. Furthermore, the patient has to be examined for the presence of other clinical features of the mentioned syndromes. Yet, there is no consensus as to laboratory tests, imaging studies, or molecular tests that should be performed in every patient with pheochromocytoma and his/her relatives in order to detect the genetic syndrome. For example, according to Bryant, all patients with phaeochromocytoma should have genetic counselling in order to detect germline mutation, and the counselling should cover, in particular, patients who are young, patients with multifocal pheochromocytoma, and patients with a positive family history. At the same time, according to her, every patient with confirmed mutation in the RET proto-oncogene should undergo annual screening for the presence of phaeochromocytoma [11]. As stated by Mathens et al., annual screening for phaeochromocytoma should be recommended in the case of RET mutations in codons 918, 634, and 630 starting from the age of ten. In the remaining mutations it should begin by the age of twenty [22]. It is worth mentioning that more than ten years passed from the moment of recognition pheochromocytoma in P.K. until the recognition of the tumour among her relatives and making a final diagnosis of MEN 2A in all of them. The liver lesions in P.K. initially raised the suspicion of metastases; however, phaeochromocytoma related to MEN 2A is less likely to give metastases than sporadic pheochromocytoma [1]. Although phaeochromocytoma can be asymptomatic, in certain situations it can lead to a catecholamine crisis, as it had in the case of M.K. Catecholamine crises are lethal in up to 50% of cases. Therefore, every case of sudden hypertensive crisis or cardiomyopathy, especially in young people, should raise the suspicion of phaeochromocytoma and be followed by appropriate diagnostic tests.

Medullary carcinoma of the thyroid is the second classic manifestation of MEN 2A. It is the most common pathology related to the syndrome — it concerns almost 100% of MEN 2A patients and it is usually multifocal [24]. Meanwhile, 25% of all medullary carcinoma cases are familial [25]. Interestingly, thyroid carcinoma was not the first manifestation of MEN 2A in the described family, as is the case for the majority of MEN 2A patients. The diagnostic process for the presence of medullary carcinoma was initiated when the pheochromocytoma turned out to be familial and when RET proto-oncogene mutation was detected in the patients. All the patients had an elevated level of calcitonin in the plasma. In every case, the final diagnosis of medullary carcinoma was made based on histopathological examination of the removed thyroid. In all patients the cancer was multifocal. The mutation in codon 634 is particularly related to high aggressiveness of the medullary carcinoma [26]. The detection of this mutation in the family requires searching for its presence in every newborn child in the family. If it is found, total thyroidectomy should be performed before five years of age because, according to the available literature, metastases can be revealed when a child is 5–6 years old [2]. In the presented family, no cancer invasion to the lymphatic nodes of the neck nor metastases to distant organs had been stated until that time. The postoperative level of calcitonin in the plasma remains undetectable in all of the family members (Table I).

Primary hyperparathyroidism is the third typical element of MEN 2A. It concerns 20–30% of all MEN 2A patients; however, its prevalence within one family can vary [8, 27]. The mutation in codon 634 particularly predisposes to its development. PHP in MEN 2A usually begins with hyperplasia of the parathyroids and can be followed by the development of one or multiple adenomas. In the majority of cases it is asymptomatic at the moment of recognition [27]. Patient age at the time of diagnosis is relatively young; the majority of them are less than 35 years old [8, 25]. RET proto-oncogene carriers have to be screened for the presence of PHP even if there are no biochemical or clinical manifestations of hyperparathyroidism. According to American Thyroid Association (ATA), screening should begin by the age of eight years in persons carrying a mutation in codon 630 and 634. In the case of other MEN 2A mutations, screening is recommended from the age of 20 years [2]. The check-up includes annual plasma calcium evaluation. Interestingly, in the described family, PHP has not yet been detected despite the mutation in codon 634. Nevertheless, the patients undergo typical annual screening towards hyperparathyroidism.

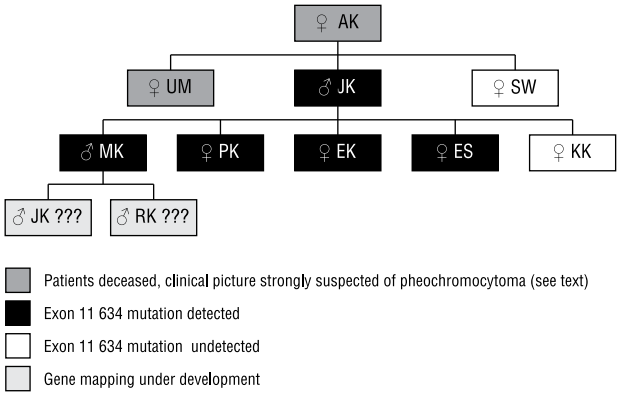

Figure 5. *Pedigree of the affected family*
Rycina 5. *Drzewo genealogiczne rodziny K*

Conclusions

Phaeochromocytoma is a rare and potentially lethal disease if a catecholamine crisis develops. Its recognition requires further investigation towards genetic syndromes, particularly MEN 2A. MEN 2A should be considered in particular in the case of bilateral phaeochromocytoma detected in young age. The detection of RET proto-oncogene mutation in a patient is an indication for the genetic screening of their relatives.

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