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MODERN MANAGEMENT OF ADRENAL TUMOURS: FOCUS ON SDHB MUTATION-RELATED PHEOCHROMOCYTOMA

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Pheochromocytoma (PHEO) and paraganglioma (PGL) are tumours that originate from neural crest cells. PHEOs arise from adrenal medulla. Although the majority of the tumours are sporadic, these can also be developed as an element of hereditary syndromes in a percentage of 30%-40% of patients. It was described a number higher than 20 genes that are involved in PHEO and PGL. The most frequent germinal mutations which predispose for PHEO are found in von Hippel-Lindau (tumour suppressor gene), RET proto-oncogene in multiple endocrine neoplasia type 2 (MEN 2), neurofibromatosis type 1 (NF-1), Myc-associated factor X (MAX), TMEM 127, whereas the A,B,C,D subunits of the mitochondrial succinate dehydrogenase complex (SDHA, SDHB, SDHC, SDHD), succinate dehydrogenase assembly factor 2 (SDHAF2) and hypoxia-inducible factor 2α (HIF2A/EPAS1) are more susceptible to PGL. In this narrative review of literature we focus on SHDB mutations underling PHEO among adrenal tumours. The genetic mutations of the SDH complex are the most implicated in patients with PGL, predominantly the SDHD gene, followed by SDHB and SDHAF1 genes. It is well known that SDHB mutations penetrance is incomplete and influenced by age. On the other hand, the SDHD mutations lead to PGL only from paternal transmission. At first, it was thought that SDHB and SDHD germline mutations penetrance was very high, approximately 70%-80% by the age of 50 years old, with a higher overall penetrance in SDHD. Once genetic testing has gotten a broader number of applications, the penetrance has fallen, especially for SDHB, reaching a level below 50% during a lifetime. Germline mutations in SDHB gene are responsible for about 10% of PHEOs/PGLs. At this time, these are associated with the most aggressive behaviour with increased metastasis incidence and lethality. Taking into consideration the high prevalence of genetic mutation and the unfavourable behaviour that some of them could have, all individuals with PHEO/PGL should test for a hereditary aetiology, especially young patient with positive family history, multifocal PGL or bilateral PHEO. Even a small percent of patients with non-familial PGL bears occult germline mutations in SDHx.

Keywords: adrenal tumour, pheochromocytoma, SDHB mutation, adrenal, adrenalectomy, paraganglioma

INTRODUCTION

Pheochromocytoma (PHEO) and paraganglioma (PGL) are tumours that originate from neural crest cells. PHEOs arises from adrenal medulla, while PGLs are split up in head and neck paragangliomas (HNPGL) which occur from parasympathetic tissue and sympathetic paragangliomas (SPGL) developed along the sympathetic chain in the thorax, abdomen and pelvis [1,2,3]. It is well known that these are rare tumours, with an incidence between 2 and 8 per million, and prevalence between 1:2500 and 1:6500. PGLs and PHEOs reach their highest point between the 3rd and 5th decades of life, with 20% of cases in children [4]. Although the majority of the tumours are sporadic, these can also be developed as an element of hereditary syndromes in a percentage of 30%-40% of patients [5,6,7]. It was described a number higher than 20 genes that are involved in PHEO and PGL [8,9,10]. The most frequent germinal mutations which predispose for PHEO are found in von Hippel-Lindau (VHL) tumour suppressor gene, RET proto-oncogene in multiple endocrine neoplasia type 2 (MEN 2), neurofibromatosis type 1 (NF 1), Myc-associated factor X (MAX), TMEM 127, whereas the A,B,C,D subunits of the mitochondrial succinate dehydrogenase complex (SDHA, SDHB, SDHC, SDHD), succinate dehydrogenase assembly factor 2 (SDHAF2) and hypoxia-inducible factor 2α (HIF2A/EPAS1) are more susceptible to PGL [8]. Moreover, there was reported cases of somatic mutation in some genes as NF1, VHL, RET, MAX, HIF2A/EPAS1 in 10-39% of tumours [11,12]. These genes have been classified into three clusters, namely: cluster 1 associated with pseudohypoxia pathway, cluster 2 characterized by increase kinase signalling and cluster 3, related to WNT signalling group [8,13]. The hereditary forms are characterized by an autosomal dominant transmission with incomplete penetrance and different genotype-phenotype correlations [14].

AIM

Our purpose is to introduce practical aspects on overviewing SDH mutations in pheochromocytoma.

METHOD

This is a review of literature. The data are organized in different subsections following practical points in endocrine management.

SDH MUTATIONS

The genetic mutations of the SDH complex are the most implicated in patients with PGL, predominantly the SDHD gene, followed by SDHB and SDHAF1 genes [15,16,17]. Each genetic mutation leads to a familial PGL syndrome (PGL 1-SDHD, PGL 2-SDHAF2, PGL 3-SDHC, PGL 4-SDHB, PGL 5-SDHA) [18]. On the other hand, it was also described non-familial PHEOs or PGLs that was related to germline mutations of SDHx [19]. These nuclear genes encode the four subunits of SDH, also called mitochondrial complex II, a

mitochondrial enzyme involved in the Krebs cycle oxidative phosphorylation and electron transport chain, both playing a central role in energy metabolism of the cell [20,21]. The SDH genes behave like a tumour suppressor, which means they prevent uncontrolled growth and division of the cell [20]. SDH-deficient tumours, as well as hypoxia-inducible factors (HIFs) with their overexpression, lead to activation of vascular endothelial growth factor (VEGF) and other hypoxia responsive genes, and consecutively to angiogenesis, glycolysis, erythropoiesis and tumorigenesis as a final result [22,23,24]. These findings indicate a connection between PGL/PHEO and any condition that induce hypoxia, like asthma, anaemia, sleep apnoea syndrome, congenital heart disease, chronic obstructive pulmonary disease or even high-altitude [15,23]. These theories are backed up by several findings in the past 50 years. It has been found that the incidence of PGL varies with altitude, with a prevalence of 1 in 10 humans above 2000m sea level, in contrast to low altitude where the penetrance is reduced [25,26]. Another supportive disclosure is the high frequency of carotid body tumour in inhabitants of high altitude, the most oxygen-sensitive organ of the body, with a feminine predisposition [27]. Moreover, several studies have described an association between cyanotic heart disease and PHEO/PGL [28,29,30]. One more mechanism was depicted by several studies – the deficiency of developmental apoptosis [31].

PENETRANCE

It is well known that SDHB mutations penetrance is incomplete and influenced by age [32]. On the other hand, the SDHD mutations lead to PGL only from paternal transmission [33]. At first, it was thought that SDHB and SDHD germline mutations penetrance was very high, approximately 70%-80% by the age of 50 years old, with a higher overall penetrance in SDHD [34,35,36,37]. Once genetic testing has gotten a broader number of applications, the penetrance has fallen, especially for SDHB, reaching a level below 50% during a lifetime [3,38,39,40]. Although Rijken et al. did not observe a notable difference between sexes regarding penetrance of SDHB mutations, Jochmanova et al. and Andrews et al. found that males present an early onset of initial tumor and metastases rather than females, with a better survival rate overall [1,3,41].

GENOTYPE-PHENOTYPE CORRELATIONS

Germline mutations in SDHB gene are responsible for about 10% of PHEOs/PGLs [42]. At this time, these are associated with the most aggressive behaviour with increased metastasis incidence and lethality [43,44]. SDHB-associated disease is generally discovered as a single tumour, compared to SDHD-related tumours which are usually defined by multiple PGLs [6]. Whereas SDHB mutations are associated more often with thoracic-abdominal PGLs and PHEOs, the SDHD mutations mostly determine head and neck PGLs [34,35,37,45]. Although previous literature indicate a high rate of malignancy in the SDHB mutations carriers, a recent study on Netherlands population reveals "a mild phenotype and a lower rate of metastatic disease", low altitude and high oxygen levels being one possible theory [2,18,46]. There are over 200 SDHB mutations described until now in all eight coding exons, with a higher number of missense mutations, which tend to amass in iron-sulfur cluster [18,47]. One recent study reports Arg90X, Ile127Ser, Exon 1 deletion, IVS1+1G>T, Val140Phe and Arg46X to be the most expressed mutations in SDHB germline mutations carriers, with an earlier occurrence of the disease in Arg46X and Val140Phe [3]. In paediatric population was also found exon 4 and 5 deletion beside those cited above [48]. There are other tumours related to this genetics changes. SDHB mutations carriers have the highest risk to develop renal cell carcinoma (RCC), approximately 14% according to Ricketts *et al*., in comparison to 8% for those who carry SDHD mutations and a very small percent in subjects with PGL 3 [49,50,51,52,53,54]. Gastrointestinal stromal tumours (GISTs) also occur in hereditary PGLs due to SDHA germline mutations in a higher percentage, but also in individuals with SDHB, SDHC or SDHD mutations [55]. Together they form Carney-Stratakis syndrome, which is autosomal dominant inherited and has incomplete penetrance, compared to Carney triad which include GIST, PGL and pulmonary chondromas mainly caused by hypermethylation of the SDHC gene and germline mosaicism [56,57,58]. Despite few reports available, it was established an association between SDHx mutations and pituitary tumours, which are frequently prolactinomas or somatotropinomas over 1 cm and have an aggressive behaviour [59,60].

A small number of thyroid carcinomas was also described in people with SDHx mutations, inducing the hypothesis that is a link between them [34,37,61,62]. Other tumours like breast carcinoma, Hodgkin's lymphoma, pancreatic neuroendocrine tumour and neuroblastoma were reported as "SDH-deficient tumours" without a certain cause-effect relationship between them [62,63].

CLINICAL-BIOCHEMICAL FEATURES

The clinical manifestations and, frequently, the reason for doctor appointment, are consequences of catecholamine excess. That include paroxysmal or constant hypertension as the most common symptom, accompanied by headache, palpitations, diaphoresis and anxiety [48,64,65]. More than that, patient also could experience pallor or flushing, nausea, vomiting and tremors [64,65]. These symptoms may be triggered by tyramine-rich diet (bananas, meat, fish, beer, wine, chocolate), some drugs (histamine, monoamine oxidase inhibitors, tricyclic antidepressants, nicotine, cocaine), anaesthesia, surgery, anxiety or some activities like exerciseing, curving or abdominal palpation [66].

Biochemical phenotype of the tumour induces the clinical manifestation. There are three different secretory profiles: adrenergic, the most common, which is characterized mainly by hypertension crisis, but also by the rest of the symptoms, noradrenergic, which usually leads to sustained hypertension, and dopaminergic phenotype, which is almost always asymptomatic or leads to nausea, vomiting, diarrhoea, hypotension [67,68,69,70]. Another very rare type of PGLs is biochemically silent [71].

The adrenergic phenotype characterizes mainly PHEOs, but rarely could reveal an extra-adrenal PGL, and is signalized by elevated plasma or urinary fractionated metanephrine, whereas noradrenergic secretion usually appears in extra-adrenal tumours, especially thoracic-abdominal-pelvic →

PGLs, and is identified by increased plasma or urinary normetanephrine levels [72]. The dopaminergic tumours, mostly extra-adrenal and associated with a high risk of malignancy, can be discovered based on plasma dopamine and 3-methoxytyramine (3-MT), its plasma metabolite [69,70,73,74]. Another marker for neuroendocrine tumours, chromogranin A, is very sensitive and precious for diagnosis, but also for disease progression, because it is secreted from all types of PGLs/PHEOs, inclusive silent tumours [75,76].

Patients with SDHB mutations usually have increased levels of normetanephrine and/or 3-MT, but 10% of them can also have tumours biochemically silent [77,78]. They generally present with hypertension, but an important group of patients could develop symptoms or signs related to tumour mass effect, such as pain, venous thrombosis, weight loss that usual suggest a malignant mass [77].

TUMOUR LOCALIZATION AND THERAPY

Computed tomography (CT) and, secondly, magnetic resonance imaging (MRI) are initial methods for localization of the tumour or possible metastasis. However, there are other useful imaging studies for patients to whom metastatic disease is suspected, such as ^{123}I-metaiodobenzylguanidine (MIBG), 6-^{18}F-fluoro-L-dopa (^{18}F-FDOPA), ^{18}F-fluorodeoxyglucose (^{18}F-FDG), and gallium-68 DOTATATE (^{68}Ga-DOTATATE), the choice being guided by molecular findings [13]. SDHB related tumours manifest high sensitivity for ^{18}F-FDG PET/CT and ^{68}Ga-DOTATATE than $^{123/131}$I-MIBG [79,80].

The only curative treatment remains surgery, with preoperative treatment with alpha-adrenergic receptor blockers [81]. For PGLs or large PHEOs, the treatment of choice is open resection; otherwise, laparoscopic adrenalectomy could be performed [81]. There are other treatment options for those patients for which surgery is unachievable, like local therapies (radiotherapy, radiofrequency ablation, and embolization), radionucleotide therapy with ^{131}I-MIBG or systemic chemotherapy [13]. New therapies like temozolomide or sunitinib are very promising, representing a big area of interests for patients with PGL and SDHB mutation [15,82,83].

FOLLOW-UP AND PROGNOSIS

It is well known the high risk for recurrence and metastasis to which SDHB mutation itself predispose. Both in paediatric and adult patients, the most common sites of metastases are bones, liver and lung [48,84]. For a subject that has already developed a tumor, the follow-up should be made throughout the entire life with plasma or urine levels of metanephrine and normetanephrine [81]. Regarding the SDHB carriers who haven't developed the disease yet, there is not an official guideline for the moment. It is recommended to begin screening with clinical examination, biochemical testing and imaging in asymptomatic carriers between 6 and 10 years of age for SDHB mutation, and between 10 and 15 years of age in the other SDHx mutations [85]. The follow-up after a first negative screening in asymptomatic carriers of SDHx should include clinical examination every year, biochemical investigations every 2 years and imaging by MRI every 2-3 years until 80 years of age if the patient didn't develop any SDH-related tumour [85]. The presence of SDHB mutations was associated with survival as an independent and significant factor [86]. Even though the penetrance is incomplete and the phenotype is variable, an intensive surveillance is required for early diagnosis, prompt and aggressive treatment, fewer complications and more disease-free patients [3,38,39,40,87]. Genetic counselling also is very important and it's recommended for all patients with SDHB mutation [88].

DISCUSSIONS

Modern era of medicine showed us that multiple endocrine tumours might be linked, including with the vast area of PHEO, based on common genetic background, from parathyroid glands to pituitary tumours and thyroid neoplasia [89-100]. Multiple endocrine neoplasias still represents a challenge among practitioners, and a genetics specialist is mandatory to be part of the multidisciplinary team when it comes to PHEO [101-113]. Nowadays, PHEO presentation varies and it might early recognized due to access to imaging and/or assessments as well gene assays in some regions, while in other centres, this is a late diagnostic with multiple comorbidities [114-126]. One the main aspects on integrating modern PHEO is asymptomatic and/or incidental presentation, as adrenal incidentaloma which still represents a challenging chapter in endocrinology [127-143].

CONCLUSIONS

Taking into consideration the high prevalence of genetic mutation and the unfavourable behaviour that some of them could Eugenia Petrova have, all individuals with PHEO/PGL should test for a hereditary aetiology, especially young patient with positive family history, multifocal PGL or bilateral PHEO. Even a small percent of patients with non-familial PGL bears occult germline mutations in SDHx. It is now widely established that SDHB germline mutations lead to a higher risk of metastasis development, tumour recurrence or other tumours development like GISTs or RCC and to a worse prognosis. That's why these patients need a more careful attention and a personalized management. The uncertainty of developing the disease associated with high malignancy risk tends to make patients with SDHB mutation more anxious and predisposed to depression. Genetic advice is mandatory in all SDHB-positive patients and their families.

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