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Counseling patients with succinate dehydrogenase subunit defects: genetics, preventive guidelines, and dealing with uncertainty

Margarita Raygada[*]

Kathryn S. King and **Karen T. Adams**

Program in Reproductive and Adult Endocrinology, CRC, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, USA

Constantine A. Stratakis

Program in Developmental Endocrinology and Genetics, Clinical Research Center, CRC (East Laboratories), Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, USA

Karel Pacak

Program in Reproductive and Adult Endocrinology, CRC, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, USA

Abstract

The discovery that mutations in the succinate dehydrogenase (*SDH*) complex subunit (*SDHA, B/C/D/AF2*) genes predispose patients to the development of tumors has led to the identification of a large population of patients and relatives at risk for developing malignancies. The most frequent conditions associated with these mutations are the familial paraganglioma syndromes. Other tumors that are frequently associated with *SDH* mutations (*SDHx*) are gastrointestinal stromal tumors and renal cell carcinomas. A number of other rare associations have also been described. SDHx mutations are often clinically silent and metastatic, but they may also be aggressive in their presentation. The penetrance of these mutations is beginning to be understood, and the characteristics of the phenotype are being elucidated. However, the inability to accurately predict the appearance, nature, and location of tumors as well as their tendency to recur or metastasize pose challenges to those who counsel and manage patients with SDHx mutations. In this work, we present our approach for counseling these families in the context of the current uncertainties, while striving to maintain patient autonomy.

Keywords

counseling; paragangliomas; pheochromocytoma; subunits; succinate dehydrogenase

[*]**Corresponding author: Margarita Raygada**, Eunice Kennedy Shriver National Institute of Child Health and Human Development Section on Developmental Genetics, 10 Center Dr MSC 1831, Room # 10D36A, Bethesda, MD 20892-1831, USA, Phone: +(301)451-8822, Fax: +(301)480-7557, Raygadam@mail.nih.gov.

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Introduction

An increasing number of families with mutations that lead to paraganglioma (PGL) syndromes are being identified since the description of the causative genetic defects, starting more than two decades ago (1). Our knowledge on the diagnosis and management of these disorders continues to improve, and more evidence regarding the natural history and the progression of these disorders is now available. However, the uncertainties about prognosis, morbidity, and mortality are still significant. Thus, helping patients cope with this diagnosis while keeping them active in the management of their condition continues to be a challenge. We present in this study our approach to a comprehensive counseling model, which includes patient education, psychosocial interventions and service delivery, for this population. Our discussion underscores the benefits of risk assessment, genetic testing, and educating patients on the importance of being actively involved in preventive and screening guidelines. In addition, we illustrate the importance of individualized preventive and screening guidelines for this group of disorders.

PGLs are tumors that originate from the chromaffin cells of the embryonic neural crest; these cells are distributed from the middle ear/skull to the pelvic floor. Based on their anatomical location and function, PGLs can be divided into two categories. The first category includes extradrenal tumors of the head and neck (HNPGLs) usually located at the carotid bifurcation, along the vagal nerve, in the jugular foramen, or in the middle ear space. The second category includes tumors located below the neck, which are most commonly found in the adrenal medulla (also known as pheochromocytoma; PCC), else-where in the abdomen, urinary bladder, and the upper mediastinum (2). The prevalence rates of these tumors are approximately 1:4500 and 1:1700, respectively, with an incidence of 3–8 cases/1 million per year in the general population (3).

PGLs/PCCs present in both hereditary and sporadic forms; there are ten genes that are involved in the pathogenesis of this condition. These include REarranged during transfection (*RET* [MIM 164761]) proto-oncogene, von Hippel-Lindau disease tumor suppressor gene (*VHL* [MIM 193300]), neurofibromatosis type 1 tumor suppressor gene (*NF1* [MIM 162200]), genes encoding the succinate dehydrogenase (*SDH*) complex subunits (*SDHB*, *SDHC*, and *SDHD* genes), the gene encoding the enzyme responsible for the flavination of the *SDHA* subunit (*SDHAF2* or *SDH5* gene) (4–8), the tumor suppressor gene *TMEM127* [MIM 613403] (9), and the Myc associated factor x gene (*MAX* [MIM 154950]), which are responsible mostly for sporadic PCCs (10). About 30%–35% of PCCs are due to mutations in these genes (11). Among the SDH genes, the first association with hereditary PGLs was identified for *SDHD* (5); this finding led to description of the other *SDH* subunit gene mutations. At this time, we know of four well defined PGL syndromes; PGL1 on 11q23.1 (12–15), PGL2 on 11q12.2 (13, 16, 17), PGL3 on 1q23.3 (8), and PGL4 on 1p36.1-p35 (4). The co-ocurrence of both PGLs and PCCs is well documented in these syndromes (18). *SDHD*, *SDHAF2*, *SDHC*, and *SDHB* are responsible for PGL1 (MIM 602690), PGL2 (MIM 601650), PGL3 (MIM 602413) and PGL4 (MIM 185470), respectively.

Mutations in the *SDH* subunit complex are inherited in an autosomal dominant manner with age-dependent and incomplete penetrance. However, mutations in the *SDHD* gene show a

parent-of-origin effect (suggestive of maternal imprinting) (14, 19). PGL syndromes and other hereditary syndromes that involve predisposition to PGLs and PCCs are associated with high morbidity and significant complications, which lead to decreased lifespan and quality of life. Hence, early screening and therapeutic interventions are essential in improving disease management. However, the expression of the phenotype is variable and the penetrance of these mutations has not been clearly defined. In addition, other tumors [e.g., renal, neuroblastoma, and gastrointestinal stromal cell tumors (GIST)] have been associated with *SDH* mutations (20–23). These factors make it difficult to define the natural history and phenotypic characteristics of these mutations; therefore, the counseling of patients is filled with uncertainties. We describe here our approach to counseling 164 families with *SDHB/C* and *D* mutations who represent a clinically heterogeneous group. Our focus during each counseling session was centered on four main goals: to provide patients with new perspectives on their understanding of the disease, increase patient's control over their condition, provide accurate information, and improve management of the disease.

Materials and methods

Participants

Both affected and unaffected family members were seen at the clinical center of the National Institutes of Health (NIH). Of the 293 patients tested at our facility, 246 had mutations in the *SDHB* gene (83%), 16 in *SDHD* (5.4%), and one in *SDHC* (0.3%). A total of 164 patients from this group were given one-on-one counseling (159 with *SDHB*, four with *SDHD*, and one with *SDHC* mutations; Figure 1). Individual medical and family histories were recorded during counseling, and all patients had been previously tested or evaluated to rule out *VHL*, *MEN2*, and *NF1*. All participants met with a genetic counselor and underwent pre- and post-test counseling for *SDHB/C/D* gene defects. The initial contact with a family was made through an affected family member (typically the proband) who presented with either PGL(s), PCC(s), or both. Upon confirmation of *SDH* subunit mutations on the proband, letters were sent to relatives (with proband's permission) for elective genetic counseling, testing and screening if positive.

Genetic analysis

The sequencing of *SDHB/C/D* was performed by Mayo Clinic Laboratories. Genetic testing through NIH involved assessment for mutations or large deletions in the *RET* protooncogene, the *VHL* gene, and subunits *B*, *C*, and *D* of the *SDH* complex. Investigation for the more recently discovered *SDHA*, *SDHAF2*, and *TMEM127* genes were not performed. Genotyping was performed in collaboration with several laboratories, including the Mayo Clinic in Rochester, Minnesota, USA, and the Department of Genetics of the European Georges Pompidou Hospital, Paris, France.

Genetic counseling procedures

The genetic testing of the different mutations associated with PGLs was done based on clinical presentation, medical and family history, and previous testing of relatives. Guidelines for testing patients with suspected PGL/PCC has been previously described in detail (24–26). The approach for managing and counseling PGL patients included several

one-on-one in-person sessions with the patient (or family members). These meetings were divided into two categories, namely, pre-test and post-test.

Pre-Test—This was done to ensure that the person understood the implications of a positive test, and that he or she had enough balanced information to be able to formulate a truly informed consent. This session included an explanation of why the test was being offered, how the results might alter the individual's life, general information about the genes being tested, possible outcomes of tests, and brief discussion on management techniques to be discussed further if results are positive. During this initial session, we also addressed any misconceptions regarding the disease, prognosis, etiology, and management.

Post-Test—For positive patients, we discussed diagnosis, prognosis, assessment of the understanding of current treatment and/or management, explanation of recurrence risk, testing of relatives, future options (including prenatal diagnosis for younger patients), and coping with the results. All patients who tested positive were counseled extensively on the implications of the results, and were given screening and preventive guidelines according to their age group and mutation/disease status. This session lasted between 1 and 2 h depending on the patient's need for questions. In this part of the session, the focus was to allow patients to express emotions, doubts, and fears about the implications of the test results. The information part of the session was used to explain and discuss in detail the preventive and screening guidelines.

Results

A total of 49 probands were seen initially for clinical evaluation, counseling, and testing. Letters were sent to 278 unaffected relatives notifying them of the risk and offering mutation analysis; 248 unaffected family members elected to be tested (80 were tested and counseled on other centers) and only four declined testing. A total of 164 patients were found to have mutations, and out of this group, 21 were found to have tumors (PCC/PGL) by imaging studies (12.8%). The four relatives who declined testing gave the following reasons: they had no offspring and did not want to know for themselves, they had other chronic health conditions and did not want to deal with more health information now, or they did not want to participate unless it helped their relative's current health. All patients expressed an improvement over worries and concerns after post-testing counseling, stating that the preventive and screening guidelines were helpful and provided a frame for management of the disorder.

Family history

Out of the total 49 probands counseled at the NIH, 33 family histories were obtained; the rest of the histories were incomplete or provided inaccurate information. All 33 family histories were from probands of *SDHB* mutation-positive families. In our sample of families from *SDHB* probands, the following incidences were reported for associated cancers (Table 1): four families reported relatives with colon cancer (12%), seven families reported pancreatic cancer (21%), one family reported thyroid cancer (3%), 12 families reported breast cancer (36%), four families reported neuroblastoma (12%), three families reported

uterine cancer (9%), and four families reported ovarian cancers (12%). In this study, we did not control for known risk factors or tested for other mutations associated with hereditary cancer syndromes (ongoing studies are addressing these issues).

Observations and recommendations

In this patient population, most of the emotional burden was focused on the uncertainty of the appearance of tumors (for those who were asymptomatic/no tumors) and risk of malignancy (for those with tumors).

Based on our experience with counseling this group of patients, we can derive several observations and recommendations, which are listed below.

- The critical component of the genetic counseling process in this group was determination and communication of risk (including risk of malignancy).
- The information collected from each patient should include a thorough personal medical history not targeted to PGL-related symptoms. Seemingly unrelated findings proved to be valuable information for risk assessment as well as the indentificaton of additional risk factors.
- Family history should comprise data from at least four generations with targeted questions, in order to elicit the necessary information for risk assessment and identifications of individuals at risk. Pedigree should be updated as additional information becomes available.
- Several misconceptions were identified at the initial pre-test sessions. The most common ones include the following:
  - the belief that if a mutation is idenfied in a person, his/her prognosis will be exactly the same as their affected relative;
  - perception of risk is higher than actual risk for both penetrance and risk of malignancy; and
  - The belief that the mutation is more penetrant in younger generations.
- Education regarding the genetics of PGL syndromes, and discussions on preventing and screening options proved to be most beneficial. All patients, except one (see below) reported reduction of anxiety, increased sense of control, improved accuracy of perceived risk, and increased knowledge about the condition.
- A small subset of patients (2/164) was more vulnerable to testing distress and demonstrated excessive anxiety upon receiving test results. They required additional counseling sessions aimed at identifying their adapting techniques, and coping strategies.
- Patients who presented with tumors and were found to have a deleterious mutation in one of the *SDH* genes were mostly concerned with risk of malignancy. This concern was more evident in the *SDHB*-positive group due to the increased risk of malignancy.

- Unaffected family members who were found to have a mutation were mostly concerned with risk of appearance of tumors and passing the mutation on to their offspring.
- Frustration about uncertainty of recurrence/malignancy was reduced by emphasizing the importance of following preventive and screening guidelines (e.g., imaging, blood & urine tests).
- Surprisingly, knowledge of carrier status of *SDH* mutations did not deter young couples/patients from having a desire to conceive in the future. Therefore, prenatal counseling was an important part of our study; we had one couple who conceived successfully through in-vitro fertilization with prenatal-genetic diagnosis.
- In total, there were four couples with one partner identified as a carrier of an *SDH* mutation (one with metastatic PGL/PCC). All four couples expressed the desire to conceive and requested prenatal counseling. They all reported gaining benefits from this session.
- One out of 164 patients decided not to implement any preventive guidelines and screening measures in her two positive offspring due to concerns that it will disrupt their life, bring anxiety, and remind them of the disease. Additional counseling sessions were scheduled with this family, along with referrals to local specialists.

Discussion

This paper describes the NIH approach for genetic counseling of those who are part of the PGL/PCC patient population who undergo *SDH* testing. Based on our observations of 164 mutation positive patients, we found that providing patients with structured preventive and screening guidelines (see supplemental information) according to their mutation/disease status decreased anxiety and gave them an increased sense of empowerement.

The information that we gathered from 33 family histories yielded high rate of reported cancer cases (Table 1). The presence of thyroid, pancreatic, breast, and renal cancer in families with *SDH* mutations has been noted before (23, 27–31). In our study, the incidence of these tumors in the patient population is higher than in other studies. One explanation for this may be that our patients are ascertained through affected relatives, indicating that our sample may reflect a more homogeneous population. Future studies are on the way to further caharacterize the family history in a more extensive number of patients with *SDH* mutations, and patients with other mutations that predispose to PGLs and PCCs.

The counseling sessions were aimed at exploring the impact of the diagnosis on both affected and unaffected family members, assisting families and individuals as they adjusted to the diagnosis, and collecting pertient medical information to set the basis for future studies.

The information is complex; thus, we focused our approach in making it personally relevant to the patient, while addressing their emotional concerns and reactions as needed. During this part, it was imperative to engage patients in the process of cognitive assimilation of genetic information so that they can understand and organize the information in terms of their respective values, beliefs, and lifestyles. There are no established genetic counseling guidelines for *SDH* mutation carrier. Our counseling approach was based on the information gathered from review of the studies on this patient population and our own studies. This part proved to be the most challenging due to the following factors: lack of explicit guidelines in the literature, lack of knowledge of physicians taking care of these families, and the need for different screening and preventing guidelines according to the stage of disease, mutation, and other factors (see above; counseling guidelines). These measures are important because of the uncertainty associated with them and the lack of means by which to accurately predict the appearance and location of tumors and their tendency to recur. In addition to informed decision-making regarding genetic testing, we were primarily concerned with decreasing anxiety, increasing the patient's sense of control, and improving accuracy of risk perception.

If left untreated, PGLs can result in significant clinical morbidity and mortality. Thus, early treatment and the identification of individuals who have higher risks for PGLs are thus imperative. The counseling approach highlighted here is aimed at improving adherence to screening recommendations, which then decreases morbidity and mortality. The clinical manifestations of PGLs are broad, and the majority of symptoms can mimic minor ailments (e.g., headaches, palpitations). Therefore, once a mutation has been identified, individuals should be monitored closely with a lower threshold for further evaluation of symptoms by a physician. Many studies are currently being conducted to characterize further the genotype-phenotype correlations, with the hope that more specific guidelines can be generated for this patient population.

Practice implications

Genetic counselors can effectively counsel these patients by providing specific preventive and screening guidelines according to the type of mutation, tumor, stage, and/or patient's clinical presentation (see supplemental information). In addition, it is important to address the uncertainty of the appearance of tumors (for patients who are asymptomatic/no tumors) and risk of malignancy (for patients who have tumors). In our patient population, anxiety towards this uncertainty was decreased by providing specific screening and preventive plans that address their particular situation. We offer further guidelines for genetic counselors and points to consider when working with patients who have *SDH* mutations. The information is complex, and counseling should be personally relevant to the patient, while addressing their emotional concerns and reactions as needed.

Study limitations and future recommendations

For genetic counselors who work with these patients, there are unique challenges that remain, and guidelines will change as we move forward with research. Our study was limited by the the small sample size, the ascertainment of patients through affected probands, and the lack of a quantitative study design based on these qualitative data. These limitations will be addressed in future studies with larger sample size. Future research

should also be aimed at further characterizing the genotype-phenotype correlations with the hope that more specific guidelines can be generated for this patient population. This is the first publication of counseling patients with *SDH* mutations, and as such, we have provided valuable insights and recommendations when dealing with this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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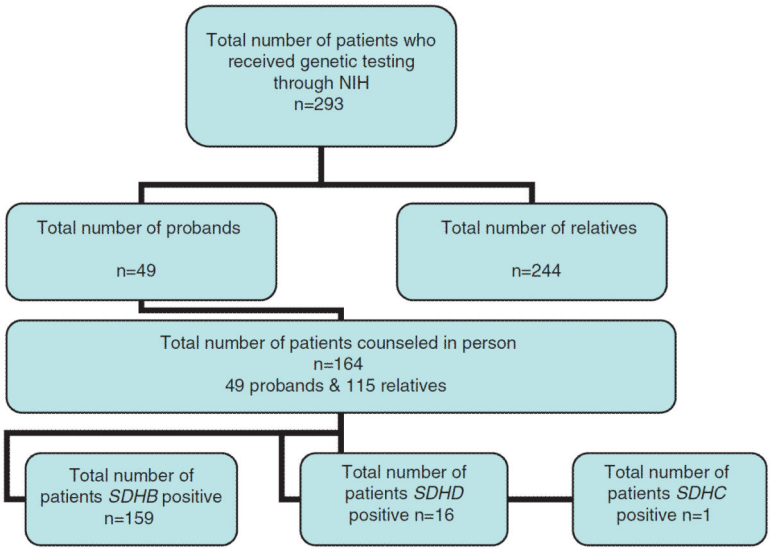

Figure 1.

Flow chart of the patient population who received genetic testing and genetic counseling at NIH.

Table 1

Family history of 33 probands with *SDHB* mutations and the number of reported cancer cases.

Type of cancer	Colon cancer	Breast cancer	Thyroid cancer	Neuroblastoma	Pancreatic cancer	Uterine cancer	Ovarian cancer
Number of cases	4	12	1	4	7	3	4
Percentage of total families	12%	36%	3%	12%	21%	9%	12%

Table 2

Penetrance by age.

SDHB	40% by age 40	70% by age 60 years	Bardella et al. (32); Benn et al. (33); Raygada et al. (1)
SDHC	38%–60% will develop PGL by age 35 years		Raygada et al. (1)
SDHD	50% by age 40 years	80% by age 60 years	Bardella et al. (32); Benn et al. (33); Raygada et al. (1);

Table 3

Clinical manifestations.

Phenotype	SDHB	SDHC	SDHD	References
Multiple primary tumors	Not commom	Not common	Common	Raygada et al. (1); Pasini and Stratakis (25)
Single primary tumors	Common	Common	Not common	Raygada et al. (1); Pasini and Stratakis (25)
Extra adrenal tumors	Common (50%–67%)	Less common	Less common (18%–21%)	
HNPGL	Less common (27%–31%)	Common	Common (71%–89%)	Niemann et al. (8)
Risk for malignancy	High (34%–37%)	Low	Low (8%)	Bardella et al. (32); Benn et al. (33);

Note: Many studies are still analyzing data and associated risks may change as more cases are reported.