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EDITORIAL

Asymptomatic carriers of mutations in succinate dehydrogenase (SDHx) genes. In search of consensus for follow-up☆

Portadores asintomáticos de mutaciones en los genes de la Succinato Deshidrogenasa (SDHx). Al encuentro del consenso para su estudio inicial y seguimiento

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Mutations in succinate dehydrogenase (SDHx) genes that encode subunits of the enzyme succinate dehydrogenase (SDHA, SDHB, SDHC and SDHD) were first associated with a predisposition to develop pheochromocytoma/paraganglioma (Pheo/PGL) in 2000. In the past decade, other mutations such as SDHAF2 have been reported.[1] Now that access to genetic testing has improved, current estimates suggest that 40%–50% of cases of Pheo/PGL are hereditary and that half are due to mutations in SDHx.[1] These mutations can be associated with the development of other tumours such as renal carcinomas, gastrointestinal stromal tumours (GISTs) and pituitary adenomas. Therefore, the current guidelines for managing Pheo/PGL recommend genetic testing for all patients with this diagnosis.[2,3] Given that most cases of SDHx mutation have an autosomal dominant pattern of inheritance, the recommendation for genetic screening extends to all first-degree relatives of the index case.[2,3]

Screening of relatives identifies carriers of genetic abnormalities, the majority of whom are asymptomatic. Early identification yields potential clinical benefits, as it enables diagnosis of smaller tumours with lesser metastatic involvement, resulting in lower mortality rates and better survival. To achieve such benefits, protocols for early detection of tumours in this carrier group must be in place. The management of these asymptomatic carriers is a clinical challenge, since different pathogenic variants of SDHx are associated with different types of inheritance, different tumour penetrance, different single or multiple tumour locations with variable distribution from the base of the skull to the pelvic floor, different functional capacity and secretory activity, and different risks of malignancy.[4] In addition, when proposing a suitable screening protocol, the implications for psychology and quality of life resulting from subjecting a

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healthy person to repeat medical appointments, radiological examinations and laboratory tests have to be taken into account. Iatrogenic consequences of radiation exposure and false positives in imaging studies must not be overlooked. Resource use must also be considered.

Deeper knowledge and understanding of the genetic basis of disease and clinical experience accumulated in the past decade have resulted in greater awareness of the characteristics of each mutation.[5,6] Hence, it is currently established that the clinical surveillance strategy must be adapted to the specific SDHx gene mutation.[4,7] There have also been advances in diagnostic imaging techniques for tumour localisation. Therefore, in recent years, several groups have recommended various protocols for regular screening that include clinical evaluation, clinical chemistry tests and different combinations of imaging studies.[7–11] Despite this, debate persists as to the management of these patients, including the age at which examinations are to begin, the type of imaging study that is to be performed, the frequency of examinations, the duration of follow-up and the conclusion thereof.

A recently published international consensus for initial screening and follow-up of asymptomatic carriers of SDHx[12] mutations was essentially based on expert opinion collected by means of a Delphi questionnaire, since, given the limited frequency of these tumours and the short period of time in which knowledge of them has been acquired, the use of the various existing protocols is not based on solid evidence. In this questionnaire, completed by 29 experts in various specialisations from 12 countries on four continents, several matters of debate were agreed upon, such as when screening should begin, which examinations should be conducted initially and in follow-up, and when follow-up should conclude.

This document proposes that tumour screening is to begin at six to 10 years of age in asymptomatic SDHB mutation carriers, given the higher risk of malignancy associated with this mutation, while in SDHA, SDHC and SDHD mutations, screening should begin at 10–15 years of age. Regarding initial screening methods, the same type of screening is recommended for all mutations: suitable clinical evaluation using a standardised questionnaire, measurement of blood pressure, determination of metanephrines and normetanephrines, and imaging studies. Those recommended as first-line imaging studies are magnetic resonance imaging (MRI) of the head, neck, chest, abdomen and pelvis in both children (<18 years of age) and adults, and positron emission tomography/computed tomography (PET/CT) (without specifying a tracer to be used) in adults with a lower level of agreement. After a negative initial study, the document proposes follow-up including clinical evaluation and measurement of metanephrines and normetanephrines every year in adults and every other year in children and whole-body MRI every two to three years. In negative studies, it is recommended that the same protocol be followed up to 70 years of age and that examinations then be spaced out to every five years until age 80, at which point follow-up would conclude.

The authors themselves indicated that this consensus serves as a starting point that can be adapted to different scenarios, stressing its importance in unifying clinical practice in these patients' management. In this regard, the multiple endocrine neoplasia (MEN), pheochromocytoma and paraganglioma group of the Endocrinology area of the Sociedad Española de Endocrinología y Nutrición [Spanish Society of Endocrinology and Nutrition] (SEEN) conducted a literature review and used its own (unpublished) follow-up data[13] to establish a protocol for evaluation of carriers of mutations in SDHx that adds some considerations to the published consensus. First, given the evidence on varying follow-up depending on the mutation present, specific differential follow-up for each mutation is proposed. Second, measurement of 3-methoxytyramine is incorporated into clinical chemistry testing. This substance is pathologically elevated in a higher percentage of cases of PGL associated with mutations in SDHB and SDHD and carries prognostic value.[14] Concerning age of onset, in mutations in SDHC and SDHD, it is proposed that clinical evaluation begin at least five years prior to the earliest age of onset of presentation in the family or at the age of 10, and that MRI begin at age.[15] In mutations in SDHB, given their more aggressive nature, we propose moving up the start of clinical and clinical-chemistry evaluation to the age of five and the start of morphological evaluation to the age of 10. With respect to functional studies, unlike the international consensus, we propose PET/CT as initial screening only for SDHB mutation, using 68Ga-DOTA-SSAs or, failing that, 18F-FDG as a tracer, as proposed by the guidelines of the European Association of Nuclear Medicine[15] and other authors.[4,16] In addition, non-contrast-enhanced whole-body rapid-sequence MRI has already been found to require less examination time than MRI of the head, neck, chest, abdomen and pelvis and to yield the same results; hence, it is preferentially recommended.[17,18]

In the coming years, prospective studies, many of which will feature the use of these follow-up protocols, will result in the availability of more conclusive data, thus enabling said protocols to be evaluated and updated periodically.

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