Head and neck paragangliomas : genetics, heredity and clinical characteristics

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Chapter 4

Genetic and clinical characteristics of Dutch paraganglioma patients

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Summary

Objective. Head and neck paragangliomas (HNPGL) are associated with mutations in genes encoding subunits of succinate dehydrogenase (SDH). The aim of this study was to evaluate SDH mutations, family history and phenotypes of patients with HNPGL in the Netherlands.

Design. We evaluated the clinical data and the mutation status of 236 patients referred between 1950 and 2009 to the Leiden University Medical Center.

Results. The large majority of the patients carried mutations in SDHD (83%), and the p.Asp92Tyr Dutch founder mutation in SDHD alone accounted for 72% of all patients with HNPGL. A mutation in SDHAF2 was found in 4%, mutations in SDHB in 3% and a mutation in SDHC was identified in a single patient (0.4%). Over 80% of patients presented with positive family history, of whom 99.5% carried a mutation in an SDH gene. SDH mutations were also found in 56% of isolated patients, chiefly in SDHD (46%), but also in SDHB (8%) and SDHC (2%). The clinical parameters of these different subgroups are discussed: including the age at diagnosis, associated pheochromocytomas, tumor multifocality and malignancy rate.

Conclusion. The majority of Dutch patients with HNPGL present with a positive family history, in contrast to other European countries. The clinical characteristics of patients with HNPGL are chiefly determined by founder mutations in SDHD, the major causative gene in both familial and isolated patients with HNPGL. The high frequency of founder mutations in SDHD suggests a higher absolute prevalence of paraganglioma syndrome in the Netherlands.

Introduction

Paragangliomas are rare, slow-growing and usually benign tumors that arise in the paraganglion tissue associated with the autonomic nervous system. Paragangliomas most frequently arise in the head and neck region, where they originate from the paraganglia in the bifurcation of the carotid artery, the jugular foramen, along the vagal nerve or along the tympanic nerve[1]. The closely related tumor, pheochromocytoma, may also arise in the adrenal medulla or less frequently in the extra-adrenal orthosympathetic paraganglia of the abdomen or thorax where they are generally referred to as extra-adrenal paragangliomas. Recent studies report a positive family history in 10% to 20% of patients with head and neck paraganglioma and indicate that family history can predict aspects of the clinical presentation[2-4]. In the case of familial paraganglioma, the male-to-female ratio is higher, the age at diagnosis lower and patients present more frequently with multiple paragangliomas[5-7]. Hereditary paraganglioma syndrome is caused by mutations in genes encoding subunits or cofactors of the mitochondrial succinate dehydrogenase (SDH): *SDHA*, *SDHB*, *SDHC*, *SDHD* or *SDHAF2*[8-13]. Mutations of *RET*, *NF1* and *VHL* have also been noted in rare cases of head and neck paragangliomas (HNPGL) associated with multiple endocrine neoplasia(MEN2), neurofibromatosis (NF1) and Von Hippel-Lindau (VHL) tumor syndromes[14].

Mutations in the different SDH genes are associated with specific clinical characteristics; head and neck paragangliomas and multiple concurrent paragangliomas are most frequently observed in SDHD-linked cases, whereas extra-adrenal abdominal and thoracic paragangliomas are most frequently found in SDHB-linked cases. Mutations in SDHB, SDHC and SDHD, but not in SDHAF2, are associated with the development of adrenal pheochromocytomas[9,15-17]. Malignancy, defined as metastatic paraganglioma, is most frequently found in SDHB-linked paraganglioma syndrome, but may also occur in SDHD-linked patients[18-23]. SDH mutation-negative paraganglioma cases also show a distinct clinical profile, characterized by a late age at diagnosis and lower risk of multiple tumors[2]. It remains unclear whether there is a genetic basis for differences in initial clinical presentation between clearly hereditary cases and isolated cases in which a genetic factor is later identified. These differences could be attributed to additional, protective genetic factors or to ascertainment bias working against the clinical identification of isolated patients with HNPGL.

In contrast to other European countries, the majority of Dutch patients with HNPGL carry founder mutations, predominantly in SDHD[24,25]. It has been suggested that the

high prevalence of founder mutations in the Netherlands can be explained by a milder phenotype of paraganglioma syndrome because of the low residential altitudes[26].

Here, we evaluate family history, mutation spectrum and clinical characteristics of a series of 236 patients with paraganglioma referred to the Leiden University Medical Center (LUMC), a tertiary referral centre for paraganglioma and pheochromocytoma in the Netherlands. We characterize the clinical presentation and genetic background of these Dutch patients with HNPGL and compare this population to HNPGL populations elsewhere.

Methods

Subjects

We analyzed data on 366 consecutive patients with a diagnosis of head and neck paraganglioma who were diagnosed or referred between 1950 and 2009 to the LUMC; a dedicated tertiary referral centre for patients with paraganglioma in the Netherlands. In all cases, clinical characteristics including gender, age at diagnosis, family history, number of paragangliomas and metastatic disease were recorded. Of the 366 patients screened, 130 patients were excluded because of a lack of data on mutation status (n = 47), incomplete description of clinical data (n = 58) or uncertain diagnosis (n = 25). In total, 236 patients with head and neck paragangliomas were included in this study. The mutation analysis of some of these patients (n = 87) has been described in a previous study of SDH mutations in the Netherlands[25]. The diagnosis of paraganglioma was based on clinical and family history, otolaryngologic examination including otoscopy and laryngoscopy, magnetic resonance imaging (MRI) and/or an angiogram of the head and neck region including the skull base. In cases with resection of the paraganglioma, the diagnosis was confirmed by histopathology. From 1989, all patients with HNPGL were followed up with MRI at intervals of 1-3 years, depending on the clinical status and growth rate of the tumor (1 year for growing tumors, 2-3 years for stable tumors). Extra-adrenal paraganglioma and pheochromocytoma screening was performed using 24-h urine analysis, in duplicate, for excess catecholamines and metanephrines. From 2002, all patients with HNPGL underwent a mutation-specific screening programme consisting of biannual 24-h urine analysis in SDHAF2, SDHC and SDHD mutation carriers, and annual 24-h urine analysis combined with biannual CT or MRI of the abdomen in SDHB mutation carriers. If the result of the biochemical analysis was above the reference limit, an MRI or CT of the abdomen, chest and pelvis was performed in combination with an ^{131}I-meta-iodobenzylguanidine (MIBG) scan to visualize potential extra-adrenal paragangliomas or pheochromocytomas.

If this investigation identified a suspect lesion, a resection was performed and the diagnosis was confirmed by histopathology. In all cases of known or suspected malignant paraganglioma, the diagnosis was confirmed by histology of the tumor material in non-neuroendocrine tissue.

Mutation analysis

All patients with paraganglioma were offered mutation analysis and genetic counseling. If patients consented to DNA analysis, the *SDHB*, *SDHC* and *SDHD* genes were scanned for the presence of mutations at the laboratory for DNA diagnostics at the LUMC. All exonic and adjacent intronic regions of these genes were tested by direct sequencing using the Sanger method on an ABI 377 Genetic Analyzer (Applied Biosystems, Carlsbad, CA, USA), starting with the exon containing the known Dutch founder mutations in *SDHD* and followed by exons that had previously been found to contain pathogenic mutations in *SDHD*, *SDHB* and *SDHC* (in that order) in the Dutch population. If this initial analysis was negative, the analysis was completed by scanning the remaining exons of these genes. Mutation-negative cases were analyzed for the presence of large deletions in *SDHB*, *SDHC* and *SDHD* by multiplex ligation-dependent probe amplification (MLPA). MLPA was carried out with the P226 MLPA kit (MRC Holland, Amsterdam, the Netherlands), containing probes for all exons and the promoter of each of these genes (27 different probes), according to the manufacturer's protocol. In cases with a negative *SDHB, SDHC* and *SDHD* mutation analysis, *SDHAF2* was tested by sequencing, as recently described[12]. No DNA analysis was performed in 51 patients because the mutation type could be reliably inferred from a positive mutation analysis of the patient's family members and pedigree information. Informed consent for DNA testing was obtained according to protocols approved by the LUMC Ethics Review Board. All tumor specimens were handled according to the ethical guidelines described in the *Code for Proper Secondary Use of Human Tissue in the Netherlands* of the Dutch Federation of Medical Scientific Societies (FEDERA).

Results

Mutations and family history

A total of 236 patients with paraganglioma belonging to 124 different families were eligible for evaluation in this study, of whom 120 were men and 116 women. Of these, 80% presented with a positive family history while the remaining 20% had no known family history (Table 1).

Table 1. Clinical characteristics of head and neck paraganglioma patients with a negative *vs* a positive family history. Screening for pheochromocytomas or extra-adrenal catecholamine producing paragangliomas was performed in 158 patients.

Patient characteristics	Negative family history (n = 48)	Positive family history (n = 188)
Male/female	22/26	98/90
Mean age at onset (years) (95% C.I.)	44.0 (39.7-48.2)	38.1 (36.3-40.0)
Malignant paraganglioma (%)	1 (2)	3 (2)
Multiple paragangliomas (%)	24 (50)	137 (73)
Adrenal pheochromocytoma (%)	3/36 (8)	14/122 (11)
Extra-adrenal paraganglioma (%)	2/36 (6)	8/122 (7)

Pathogenic mutations in SDHAF2, SDHB, SDHC or SDHD were identified in 214 of the 236 patients (91%) and in 102 of the 124 different families (82%). DNA analysis or family history failed to reveal mutations in only 22 patients (9%) (Table 2). The vast majority of patients with HNPGL carried mutations in SDHD (83%), 4% carried mutations in SDHAF2, 3% in SDHB and one mutation in SDHC was identified in a single patient (0.4%) (Tables 2 and 3). The p.Asp92Tyr Dutch founder mutation in SDHD was the most common mutation, accounting for 72% of all patients with HNPGL (Table 3).

Table 2. Clinical characteristics of 235 patients with head and neck paraganglioma. A single *SDHC* mutation carrier is excluded. 'No mutation' is defined as the group of patients without a mutation in *SDHB*, *SDHC*, *SDHD*, or *SDHAF2*.

Patient characteristics	*SDHB* (n = 8)	*SDHD* (n = 195)	*SDHAF2* (n = 10)	No mutation (n = 22)
Male/female	6/2	100/95	5/5	9/13
Mean age at onset (years) (95% C.I.)	47.1 (41.2-53.0)	37.9 (36.3-39.5)	33.6 (21.3-45.9)	52.0 (46.3-57.7)
Malignant paraganglioma (%)	0	4 (2)	0	0
Multiple paragangliomas (%)	4 (50)	144 (74)	7 (70)	7 (32)
Adrenal pheochromocytoma (%)	0/8 (0)	17/127 (13)	0/5 (0)	0/17 (0)
Extra-adrenal paraganglioma (%)	0/8 (0)	10/127 (8)	0/5 (0)	0/17 (0)

Evaluating families only, SDHD mutations were found in 73%, SDHAF2 mutations in 2%, SDHB mutations in 6%, SDHC mutations in 1% and no SDH mutations in 18%. The p.Asp92Tyr mutation accounted for 75 of the 124 families (60%) (Table 3).

Table 3. Mutations identified in *SDHAF2*, *SDHB*, *SDHC* and *SDHD*. Pathogenic mutations in succinate dehydrogenase-related genes could be identified in 214 of the 236 patients (91%); 187 of which had a positive family history (87%). The 214 succinate dehydrogenase (SDH) mutation carriers belong to 102 different families.

Gene	Mutation type	Protein	Positive family history (n = 187)	Negative family history (n = 27)	Families (n = 102)
SDHAF2	c.232G>A	p.Gly78Arg	10	0	3
SDHB	c.423+1G>A	Splice site, intron 4	2	2	4
	c.201-4429_287-933del	del exon 3	1	0	1
	c.574T>C	p.Cys192Arg	0	1	1
	c.590C>G	p.Pro197Arg	1	0	1
	c.649C>T	p.Arg217Cys	0	1	1
SDHC	c.242-241_510+1978del	del exon 5 & 6	0	1	1
SDHD	c.274G>T	p.Asp92Tyr	152	19	75
	c.416T>C	p.Leu139Pro	14	1	8
	Del promoter, exon 1 en 2	Unknown	0	1	1
	c.120_121insC	p.Glu42Argfs	2	1	2
	c.169_169+9delTGTATGTTCT	Unknown	1	0	1
	c.242C>T	p.Pro81Leu	2	0	2
	c.337_340delGACT	p.Asp113fs	2	0	1

In patients with a positive family history, mutations in SDHAF2, SDHB or SDHD could be identified in 99.5% of the patients with HNPGL and 99% of the families with HNPGL. By far the most frequently affected gene was *SDHD*, found in 92% of patients with HNPGL and 89% of families with HNPGL. The p.Asp92Tyr mutation was predominant amongst the familial SDHD mutation carriers, found in 152 of 173 patients with HNPGL (88%) and in 56 of 68 SDHD-linked families (82%) (Table 3). All patients with a negative family history were found to be unrelated. Of these patients, 56% showed mutations in SDHB, SDHC or SDHD, with 46% attributable to mutations of SDHD. The SDHD p.Asp92Tyr founder mutation accounted for 86% of all SDHD-linked patients with an isolated presentation (Table 3). No patient with a negative family history had a mutation in SDHAF2.

Age at diagnosis

The mean age at diagnosis of patients with paraganglioma was 39.3 years (95% CI: 37.6-41.0). Age at diagnosis was higher in patients with a negative family history than in patients with a positive family history (44.0 vs. 38.1 years) (Table 1). Age at diagnosis also differed according to the genetic subgroup, ranging from 33.6 years in SDHAF2-linked patients, 37.9 years in SDHD-linked patients, to 52.0 years without a mutation in SDHAF2, SDHB,

SDHC or SDHD (Table 2). Within the SDHD-linked patient group, the mean age at diagnosis was comparable for patients with an isolated presentation (35.5 years; 95% CI: 30.6-40.4) and for those with a positive family history (38.2 years; 95% CI: 36.3-40.1) (data not shown). Similarly, in SDHB-linked patients, we found no significant difference between the mean age at diagnosis of isolated cases (47.3 years; 95% CI: 31.9-59.6) and that of familial cases (47.0 years; 95% CI: 43.6-50.4) (data not shown).

Multifocality

Multiple synchronous or metachronous paragangliomas were found in 162 of 236 patients with paraganglioma (69%), up to a maximum of six metachronous paragangliomas. The majority of patients with a positive family history were diagnosed with multiple tumors (73%). Significant multifocality was also present in HNPGL patients with an isolated presentation, affecting 24 of the 48 cases (50%) (Table 1), with 14 of those 24 (58%) accounted for by mutations in *SDHD*, while the remaining cases showed either mutations in *SDHB* (three of 24) or no mutation in any of the SDH related genes (data not shown).

We found a clear association between the risk of multiple paragangliomas and genetic subgroup; multiple tumors were most frequently observed in SDHD- and SDHAF2-linked patients (74% and 70% respectively) (Table 2). Within the group of SDHD mutation carriers, multiple tumors were a frequent finding both in isolated patients (14 of 22; 64%) and patients with a positive family history (130 of 173; 75%) (data not shown).

Concurrent pheochromocytomas and extra-adrenal paragangliomas

Screening for concurrent pheochromocytomas and catecholamine producing extra-adrenal paragangliomas was performed in 158 of the 236 patients with HNPGL (Tables 1 and 2). Pheochromocytomas were identified in 17 of these 158 patients (11%), extra-adrenal paragangliomas in 10 of 158 patients (6%). Pheochromocytomas were only found in patients with SDHD mutations and were present in both familial SDHD-linked patients (14 of the 113 screened patients, 12%) and in isolated SDHD-linked patients (3 of the 14 screened patients, 21%) (data not shown). Pheochromocytomas were diagnosed in 14 carriers of the p.Asp92Tyr mutation, in two carriers of the p.Leu139Pro mutation and in one patient with a deletion of exon 1 and 2 of SDHD. Extra-adrenal catecholamine producing paragangliomas were only diagnosed in carriers of the SDHD p.Asp92Tyr mutation, in eight of 113 (7%) familial cases and in two of 14 (14%) isolated cases (data not shown).

Malignancy

Malignant paragangliomas were diagnosed in only four of 236 patients (2%) (Tables 1 and 2). In three cases, the metastatic lesion was discovered on MIBG scan; in one case, the metastatic lesion was discovered on MRI. The metastatic lesion was confirmed to consist of paraganglioma tissue by histopathology of cervical lymph nodes (n = 2) or the pelvic bone (n = 2). All patients developing malignant paraganglioma carried the p.Asp92Tyr mutation in SDHD.

Discussion

In this study, we present the clinical characteristics and genetic background of 236 Dutch patients with paraganglioma, including the largest series of SDHD mutation carriers described to date. Almost 80% of Dutch patients with HNPGL have a positive family history, in contrast to various European studies (performed in France, Italy, Germany and Spain) which identified 11-23% of patients with HNPGL as familial cases[2-4]. A mutation in an SDH gene could be identified in all but one of our familial patients with HNPGL, most frequently in *SDHD* (92%). Even if family members are excluded from the analysis, *SDHD* mutations still represent 89% of paraganglioma families. Mutations in SDH genes were also identified in a surprising number of isolated Dutch patients with HNPGL (56%), contrasting sharply with the 22-25% of isolated cases previously reported to be mutation-positive[4,27].

This predominance of SDHD mutations in patients with HNPGL (82% of all patients with HNPGL and 73% of all families with HNPGL this series) accords well with a recent report on SDH mutations in the Netherlands and with mutation screening in patients with HNPGL performed elsewhere (70-75%)[2,4,24]. In contrast to the study by Burnichon et al. which identified 98 different mutations in a series of 242 mutation carriers, each accounting for a maximum of six cases, the spectrum of *SDHD* mutations in the Netherlands is limited, with only seven different *SDHD* mutations identified in the current study (Table 3)[2]. In accordance with earlier reports, we found that the most prevalent mutations in SDHD are the Dutch founder mutations p.Asp92Tyr and p.Leu139Pro (Table 3)[24,25].

The clinical characteristics found in both familial and isolated SDHD-linked patients were very similar, with a comparable low mean age at diagnosis, a high risk of multiple tumors, and a risk of concurrent pheochromocytomas or catecholamine producing extra-adrenal paragangliomas. As factors such as early diagnosis through family screening and patient

or doctor awareness do not play a role in isolated cases, these characteristics can be seen as a true feature of the SDHD-linked phenotype.

One of the hypotheses put forward to explain the remarkable clustering of SDHD founder mutations in the Netherlands proposes that the high incidence of hereditary paraganglioma syndrome can be explained by low residential altitudes[26]. The relatively high oxygen pressure at sea level was postulated to result in a milder disease phenotype, reducing penetrance and negative selection. This proposal is not supported by our data, as we found the clinical characteristics of the Dutch SDHD-linked phenotype to be comparable to other studies, including the mean age at diagnosis (37.9 vs. 24.9-35.7 years found elsewhere), the risk of developing multiple paragangliomas (74% vs. 23-74% in other studies) and a malignancy rate of 2%, compared to 0-10% found elsewhere[2,3,18,19,26,28,29]. The dominance of SDHD founder mutations in the Netherlands is therefore most probably because of socio-demographic factors. Dutch society was characterized until the middle of the twentieth century by limited intermarriage and a strong segregation by religious affiliation and socio-economic, geographic and linguistic factors. These same factors have contributed to the creation of genetically isolated populations and a high prevalence of many other founder mutations in disease-related genes in the Netherlands[30]. Carriers of the most common Dutch founder mutations share a common haplotype surrounding the mutations and therefore share a common ancestor. Coalescence time calculations have shown that the Dutch SDHD founder mutation, p.Asp92Tyr, is between 200 and 960 years old[31].

A further striking feature of paraganglioma syndrome in the Netherlands is the prevalence of the p.Gly78Arg mutation in SDHAF2, identified in 10 of 236 patients (4%) and three of 124 families (2%) in this study. It is the only pathogenic mutation of SDHAF2 currently known and has been identified in one Dutch kindred and an unrelated Spanish family[32]. All known Dutch carriers of the p.Gly78Arg mutation in SDHAF2 share a common haplotype and have been linked to a common ancestor[31,33]. Like *SDHD*, *SDHAF2* is characterized by an exclusively paternal transmission of symptomatic paraganglioma syndrome. This similarity in inheritance pattern has been hypothesized to be because both genes are located on chromosome 11 and may follow the same route to tumorigenesis[34,35]. In this study, we observed interesting clinical similarities between SDHAF2 and SDHD mutation carriers: both patient groups are characterized by a high percentage of multiple paragangliomas (74% and 70% respectively) and an early mean age at diagnosis (38 and 34 years respectively) (Table 2). However, whereas SDHD-linked patients showed concurrent pheochromocytomas in 13%, extra-adrenal paragangliomas in 8% and metastatic paraganglioma in 2%, SDHAF2 mutation carriers showed no paragangliomas

outside the head and neck region, in accordance with a recent report on a Dutch SDHAF2-linked kindred[17].

The number of HNPGL patients with mutations of SDHB found in this study is remarkably low (3% of patients with HNPGL and 6% of families with HNPGL) compared with recent studies performed elsewhere, which found 22% to 34% of all HNPGL cases to be SDHB mutation carriers[2,4]. This contrast is puzzling, but it is also reflected in the relatively low numbers of mutation-negative cases (9%). As we have recently conducted several studies focused on SDHB mutation carriers, it seems unlikely that these patients have simply escaped our attention[36,37]. This suggests that the apparent relative scarcity of both SDHB-linked and mutation-negative cases may result from excess SDHD-linked cases, compared to surrounding countries. It follows that the absolute prevalence of HNPGL may be higher in the Netherlands than in other European countries. The true prevalence of rare diseases is notoriously difficult to estimate and is prone to a plethora of acquisition biases. Nevertheless, in a recent study on SDH mutation frequencies in the Netherlands, we identified 601 SDHD mutation carriers, while recent large studies from Italy and France identified only 47 and 130 SDHD mutation carriers, respectively, despite the fact that these countries have approximately four-fold higher populations than that of the Netherlands[2,3,24]. While details of the selection and acquisition of each cohort could have a significant impact on prevalence data, the large number of Dutch SDHD mutation carriers identified and the overwhelming predominance of SDHD-linked HNPGL over SDHB and mutation-negative cases are suggestive of a significantly increased prevalence of HNPGL in the Netherlands.

In this study, we evaluate the SDH mutation status and the clinical presentation of a large series of patients with head and neck paraganglioma collected over a 59-year period. In contrast to other European countries, the majority of head and neck paragangliomas are attributable to Dutch founder mutations in SDHD, most prominently the p.Asp92Tyr mutation. SDHD mutations are also a major factor in HNPGL patients with an isolated presentation. We find that the clinical characteristics of SDHD-linked patients with an isolated presentation are identical to those of clearly hereditary cases, and the consequences of the dominance of SDHD mutations are therefore an early age at diagnosis, a high risk of multiple paragangliomas including pheochromocytomas, and an exclusive paternal transmission of disease in the large majority of Dutch patients with HNPGL. Moreover, the very high frequency of familial presentation, the high prevalence of SDHD mutations, the relatively high frequency of mutations in SDHAF2 and the relative lack of mutation-negative cases and SDHB mutation carriers all strongly suggest an increased prevalence of HNPGL in the Netherlands.

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