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CLINICAL STUDY

Quality of life is decreased in patients with paragangliomas

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Abstract

Context: Germline mutations in succinate dehydrogenase (*SDH*) genes predispose carriers for developing paragangliomas, and studies on their quality of life (QoL) are scarce.
Objectives: The objectives of this study were to assess QoL in patients with paragangliomas (PGL), to evaluate long-term QoL, and to explore potential differences in QoL between *SDH* mutation carriers and paraganglioma patients without an *SDH* mutation.
Design: Cross-sectional, case–control study.
Setting: Tertiary referral center.
Subjects: One hundred and seventy four paraganglioma patients were included: 25 *SDHB*, two *SDHC*, and 122 *SDHD* mutation carriers and 25 patients without an *SDH* mutation. They provided 100 peers as control persons. Furthermore, patients were compared with age-adjusted reference populations.
Main outcome measures: QoL was assessed using three validated health-related QoL questionnaires: the Hospital Anxiety and Depression Scale, the Multidimensional Fatigue Index 20, and the Short Form 36.
Results: Patients reported a significantly impaired QoL compared with their own controls, mainly on fatigue and physical condition subscales. Compared with age-adjusted literature values, patients had significantly impaired scores on physical, psychological, and social subscales. A decreased QoL was mainly related to paraganglioma-associated complaints.

There was no difference in QoL between the various *SDH* mutation carriers or paraganglioma patients without an *SDH* mutation. QoL in asymptomatic mutation carriers, i.e. without manifest disease, did not differ from QoL of the general population. Long-term results in 41 patients showed no alteration in QoL besides a reduced level of activity.
Conclusion: QoL is decreased in paraganglioma patients but stable when measured over time.

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Introduction

Paragangliomas (PGL) are rare tumors originating from neural crest cells and are strongly associated with the autonomic nervous system. They are divided by region in head and neck paragangliomas (HNPGLs), adrenal paragangliomas (i.e. pheochromocytomas), and extra-adrenal paragangliomas (i.e. paragangliomas in the thorax, abdomen, or pelvis).

Paragangliomas can produce excessive amounts of catecholamines, especially when located in the adrenals. The classic triad of symptoms associated with pheochromocytomas is episodic headache, sweating, and palpitations with often additional persistent hypertension. Pheochromocytomas require surgery and preoperative management with α- and β-blockade to inhibit the effects of released catecholamines, thereby preventing lethal cardiovascular complications (1).

The primary cause of morbidity in HNPGL patients is cranial nerve impairment due to proximity to the tumor. Patients complain about hearing loss, tinnitus, hoarseness, and problems in swallowing. Although surgery is an option in the treatment of HNPGLs, the risk of treatment-related additional loss of nerve function is a matter of consideration (2, 3). Therefore, considering the indolent nature of most HNPGLs, a 'wait and scan' policy may be advisable in appropriate cases (4).

Paragangliomas can occur as a consequence of germline mutations in one of the subunits of the mitochondrial complex II succinate dehydrogenase (*SDH*) gene. Mutations in subunits A, B, C, and D and assembly factor 2 have been identified (5, 6, 7, 8, 9). In The Netherlands, the p.Asp92Tyr founder mutation in *SDHD* is the most prevalent cause of hereditary paragangliomas (10). Distinct genotype–phenotype associations have been reported. *SDHB* mutation carriers seem to be at highest risk for developing malignant paragangliomas (11, 12). Possibly, this could result in a reduced quality of life (QoL) in these patients.

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In a previous case–control study from our department, Havekes *et al.* (13) reported an impaired QoL in 82 HNPGL patients with or without (a history of) paragangliomas at other locations. No differences of QoL scores were found between *SDHD* mutation carriers and paraganglioma patients who were genotyped without finding a mutation or patients who had not been tested. To the best of our knowledge, QoL has never been assessed in *SDHB* and *SDHC* mutation carriers, nor has it been compared between different groups of mutation carriers. Considering the classical maternal imprinting related to *SDHD* transmission, it would also be of interest to compare QoL scores between male and female *SDHD* mutation carriers.

In addition, no long-term data on QoL in paraganglioma patients are available and we do not know how this is affected by surgical or conservative treatment. This is important to evaluate, as QoL has become an important outcome parameter for patients as well as their treating physicians in discussing the various treatment options (14, 15, 16).

The primary objective of this study was to assess QoL in an extended cohort of paraganglioma patients. Secondary objectives were to explore potential differences in QoL between *SDHB*, *SDHC*, and *SDHD* mutation carriers and patients without an *SDH* mutation, between male and female *SDHD* mutation carriers, and to assess QoL over time.

Materials and methods

Study protocol

Patients were recruited from the outpatient clinic of the Department of Endocrinology of the Leiden University Medical Center (LUMC), a tertiary referral center for paragangliomas. We included all patients with paragangliomas, as well as asymptomatic *SDH* mutation carriers. 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 Analyser (Applied Biosystems) and MLPA was carried out with the P226 multiplex ligation-dependent probe amplification (MLPA) Kit (MRC Holland, Amsterdam, The Netherlands) (10).

In February 2012, a total of 302 patients were sent an envelope containing three validated health-related QoL questionnaires: the Hospital Anxiety and Depression Scale (HADS), the Multidimensional Fatigue Index (MFI-20), and the Short Form 36 (SF-36) (17, 18, 19, 20). Furthermore, patients were asked to fill in a questionnaire concerning possible signs and symptoms associated with paragangliomas. This questionnaire had previously been developed at our department in order to relate QoL to clinical data (13). Patients were asked to return these questionnaires in a prepaid envelope.

Non-responders were encouraged by a reminder letter to complete and return questionnaires. All questionnaires received before 1st May were included in our study.

To create a control group with similar socioeconomic status from the same geographical area, all patients received a second envelope containing the HADS, MFI-20, and SF-36 and were requested to provide a control person of similar age and sex. In addition, to compare patients with the general population, we used values derived from the literature. To measure QoL over time, we used results of the study by Havekes *et al.* (13).

This study protocol was approved by the Medical Ethics Committee of the LUMC. All subjects returning the completed questionnaires gave written consent for participation.

Study parameters

The primary parameters were the outcomes of the three validated health-related QoL questionnaires. The relations between the outcomes and patient characteristics, genetic status, number and location of paragangliomas, signs and symptoms, and treatment characteristics were examined. Longitudinal QoL was assessed.

QoL questionnaires

Hospital Anxiety and Depression Scale The HADS contains 14 questions related to two subscales: anxiety and depression. Both subscales contain seven items scored on a four-point scale, ranging from 0 to 3. Scores range from 0 to 21 for each subscale and from 0 to 42 for the total score. A higher score indicates a higher level of anxiety and depression (20). Reference values of the Dutch population were derived from Spinhoven *et al.* (21).

Multidimensional Fatigue Index 20 The MFI-20 consists of 20 statements to assess fatigue (18). Five dimensions of fatigue are measured: i) general fatigue, ii) physical fatigue, iii) reduced activity, iv) reduced motivation, and v) mental fatigue. Items are scored on a five-point scale and subscales range from 4 to 20. Higher scores are associated with a higher feeling of fatigue. General values of the Dutch population were derived from Smets *et al.* (22).

Short Form 36 The SF-36 questionnaire includes 36 items assessing general well-being/functional status during the previous 30 days (17, 19). The items are formulated as statements or questions to assess eight functional status domains: i) physical functioning, ii) social functioning, iii) limitations in usual role activities because of physical health problems, iv) pain, v) general mental health (psychological distress and well-being), vi) limitations in usual role activities because

of emotional problems, vii) vitality (energy and fatigue), and viii) general health perceptions and change in health. Scores are expressed on a 0–100 scale, with higher scores indicating a better QoL. Dutch reference values were derived from the official Dutch manual (23).

Missing data

In case of missing data, patients received the missing questions by mail with a request to complete them. As we were not in possession of postal addresses of control persons provided by our patients, we were not able to send this request to control persons.

Missing data of the SF-36 were computed per subscale by imputation of personal mean scores, in case half or less of questions within the subscale were missing (24). Imputation of personal mean scores per subscale was also used if one item or less was missing per subscale in the HADS and MFI-20. If more questions were missing, the concerning subscale was excluded from our analyses.

Statistical analysis

SPSS for Windows version 17.0 (SPSS, Inc.) was used for data analysis. Data are expressed as mean $\pm$ S.D., unless otherwise mentioned. To compare patient and control data, the unpaired *t*-test was used for normally distributed variables and the Mann–Whitney *U* test for non-normally distributed variables. To compare present QoL results with those of 5 years ago, the paired *t*-test was used for normally distributed variables and the Wilcoxon signed rank test for non-normally distributed variables. Normal distribution was tested with the Kolmogorov–Smirnov test. We used weighted means from literature reference data according to the age distribution in our cohort (25).

Subgroups of patients were compared using the one-way ANOVA or Kruskal–Wallis test. Using linear regression analysis, we assessed the effect of continuous variables on QoL. These results are expressed as the absolute standardized β of independent predictive values. *Post hoc* power was calculated using G*Power version 3.1 (Dusseldorf, North Rhine-Westphalia, Germany) (26).

Differences were considered statistically significant at $P<0.05$.

Results

Patient and treatment characteristics

Out of 302 addressed patients, a total of 174 (58%) returned the completed questionnaires. The mean age of the study population was 52 ± 14 years. The mean time between diagnosis of PGL and this study was 11.3 ± 10.0 years.

No significant difference in age, number, and localization of paragangliomas was found between responders and non-responders, although a significantly higher percentage of women was found in the responder group (60 vs 47%).

The 174 patients who completed the questionnaires provided 100 controls (57%). Mean age in the control group was 49 ± 13 years. There were no significant differences in age and sex between the study population

Table 1 Characteristics of patients and controls.

	All patients (*n*=174)	***SDHB*** (*n*=25)	***SDHC*** (*n*=2)	***SDHD*** (*n*=122)	**No *SDH* mutation** (*n*=25)	**Own controls** (*n*=100)
Age (years, mean $\pm$ S.D.)	52.2 $\pm$ 13.5	55.8 $\pm$ 14.5	48.5 $\pm$ 26.2	51.1 $\pm$ 13.6	54.4 $\pm$ 11.3	49.3 $\pm$ 12.9
Sex (M/F)	70/104	10/15	0/2	54/68	6/19	38/49[a]
Number of HNPGLs[b]						
0	28 (16%)	15 (60%)	0	13 (11%)	0	
1	43 (25%)	7 (28%)	2	13 (11%)	21 (84%)	
2	47 (27%)	3 (12%)	0	41 (34%)	3 (12%)	
$\geq$3	56 (32%)	0	0	55 (45%)	1 (4%)	
Carotid body tumor	115 (66%)	4 (16%)	1	102 (84%)	8 (32%)	
Complete resection	55 (32%)	2 (8%)	0	49 (40%)	4 (16%)	
In situ	91 (52%)	2 (8%)	1	83 (68%)	5 (20%)	
Jugulotympanic tumor	52 (30%)	6 (24%)	0	34 (28%)	12 (48%)	
Complete resection	11 (6%)	2 (8%)		7 (6%)	2 (8%)	
In situ	42 (24%)	4 (16%)		28 (23%)	10 (40%)	
Vagal body tumor	72 (41%)	1 (4%)	1	63 (52%)	7 (28%)	
Complete resection	3 (2%)	0	0	3 (2%)	0	
In situ	70 (34%)	1 (4%)	1	61 (50%)	7 (28%)	
History intra-adrenal paraganglioma	10 (6%)	0	0	10 (8%)	0	
History extra-adrenal paraganglioma	7 (4%)	2 (8%)	0	5 (4%)	0	
Intra-adrenal paraganglioma at the time of study	1 (1%)	0	0	1 (1%)	0	
Extra-adrenal paraganglioma at time of study	4 (2%)	0	0	4 (3%)	0	
Malignant paraganglioma	6 (3%)	1 (4%)	0	4 (3%)	1 (4%)	

[a]Thirteen control persons did not fill in their sex on the response form.
[b]Head and neck paragangliomas.

Table 2 QoL parameters (HADS, MFI-20, and SF-36) in paraganglioma patients compared to own controls and age-adjusted reference values.

Questionnaire	Patients ($n=174$)	Own controls ($n=100$)	*P* value	Age-adjusted reference values (21, 22, 23)	*P* value
HADS					
Anxiety	5.9±3.8	5.0±3.2	NS	4.9±3.6	<0.001
Depression	4.0±3.7	3.0±2.7	NS	3.6±3.3	NS
Total	9.9±6.9	8.1±5.3	NS	8.4±6.3	<0.005
MFI-20					
General fatigue	11.3±4.8	9.3±4.1	<0.001	9.9±5.2	<0.005
Physical fatigue	9.9±4.6	7.7±3.6	<0.001	8.8±4.9	<0.02
Reduced activity	9.3±4.0	7.6±3.7	<0.001	8.7±4.6	NS
Reduced motivation	9.2±4.0	7.8±3.4	<0.005	8.2±4.0	<0.01
Mental fatigue	10.0±4.3	8.9±4.2	<0.05	8.3±4.8	<0.001
SF-36					
Physical functioning	84.0±18.9	89.4±14.3	<0.05	78.4±22.2	<0.001
Social functioning	78.0±24.3	87.0±17.9	<0.005	86.0±20.9	<0.001
Role limitations due to physical problems	68.5±41.0	86.5±33.8	<0.001	77.6±36.7	<0.005
Role limitations due to emotional problems	79.7±35.4	86.3±33.2	NS	84.9±31.3	<0.05
Mental health	72.0±17.6	77.1±15.4	<0.05	76.8±18.5	<0.001
Vitality	60.9±20.2	66.7±17.5	<0.05	66.8±20.5	<0.001
Bodily pain	82.6±21.8	87.0±18.6	NS	79.0±25.2	<0.05
General health perception	62.7±22.9	74.5±16.9	<0.001	68.7±22.1	<0.001
Health change	50.6±20.3	52.0±16.7	NS	51.0±18.3	NS

NS, not significant; HADS, Hospital Anxiety and Depression Scale; MFI-20, Multidimensional Fatigue Index; SF-36, Short Form 36.

and controls. In the control group, one HADS questionnaire, three MFI-20 questionnaires, and two health change subscales of the SF-36 were discarded because too many questions were missing.

Detailed characteristics of patients are listed in Table 1. Within the patient group, 16% had not been diagnosed with a HNPGL, 25% with one, 27% with two, and 32% had been diagnosed with three or more HNPGLs. A carotid body tumor was the most prevalent HNPGL: 66% of patients had been diagnosed with one or two carotid body tumors. Of these patients, 55 had complete resection of one or two carotid body tumors. Jugulotympanic and vagal body tumors were less frequently found and were also less frequently surgically removed: 6 and 2% respectively. At the time of the study, one participant had a pheochromocytoma *in situ* and four participants had extra-adrenal paragangliomas *in situ*, whereas in the past 6% had been operated on a pheochromocytoma and 4% on an extra-adrenal paraganglioma. In patients in whom PGL surgery was performed, the mean time between first operation and this study was 12.4±10.8 years. Six patients were found to have malignant paragangliomas, i.e. metastatic disease. In total, 23 patients (13%) were asymptomatic mutation carriers, i.e. persons without manifest disease, as determined by surveillance for paragangliomas.

The responding patient group consisted of 25 *SDHB* mutation carriers, two *SDHC* mutation carriers, and 122 *SDHD* mutation carriers and 25 patients without an *SDH* mutation. All *SDHD* mutation carriers inherited the mutation from their father. The mean time between genetic testing and this study was 4.4±3.2 years. Out of these 174 patients, 11 (6%) had not been molecular genetically tested. Of the untested patients, eight had a positive family history with a proven *SDHD* mutation and were diagnosed with paragangliomas themselves. Therefore, they were considered to be obligate *SDHD* mutation carriers. The remaining three patients were diagnosed with a single HNPGL and over the age of 50 years. Considering the fact they did not have multiple paragangliomas or a positive family history, they were regarded as having no *SDH* mutation.

Forty-one respondents had also participated in the QoL study, which was carried out in our center 5 years earlier (13). Mean age in this group was 54±11 years and 54% were females. One patient carried the *SDHB* mutation and 36 the *SDHD* mutation. Thirty-five patients (85%) had a HNPGL *in situ*, of whom 74% a carotid body tumor, 37% a jugulotympanic tumor, and 54% a vagal body tumor. Six patients had been operated on for a pheochromocytoma in the past and two on an extra-adrenal paraganglioma. One patient had a malignant paraganglioma, i.e. metastatic disease.

QoL in paraganglioma patients compared with controls and age-adjusted reference values

Paraganglioma patients reported a significantly impaired QoL on the HADS, MFI-20, and SF-36 compared with both their own controls and the age-adjusted values derived from the literature (Table 2). Compared with own controls, patients had affected

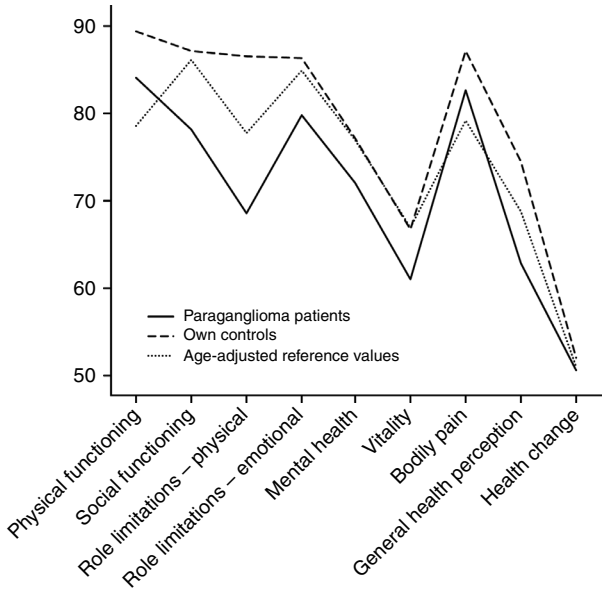

Figure 1 SF-36 results.

scores on all MFI-20 (i.e. fatigue) subscales. The SF-36 questionnaire demonstrated a decreased score on physical and social functioning, role limitations due to physical problems, mental health, vitality, and general health perception. No differences in anxiety or depression were found between patients and controls (HADS questionnaire).

Compared with age-adjusted reference values (21, 22, 23), the anxiety subscale and the total score of the HADS questionnaire were impaired in paraganglioma patients. Patients experienced an increased feeling of fatigue with four out of five subscales of the MFI-20 being increased. In the SF-36 questionnaire, all subscales were significantly decreased in the patient group except for health change (Fig. 1).

QoL in SDH mutation carriers

We aimed to explore potential differences in QoL between *SDHB*, *SDHC*, and *SDHD* mutation carriers and patients without an *SDH* mutation. As only two subjects carried an *SDHC* mutation, we excluded these *SDHC* mutation carriers from our analyses because of a lack of statistical power. Comparing QoL scores of *SDHB* mutation carriers, *SDHD* mutation carriers and patients without an *SDH* mutation revealed no significant differences on the HADS, MFI-20, or the SF-36.

Forty-four percent of the *SDHD* mutation carriers were men. Comparing QoL scores between male and female *SDHD* mutation carriers revealed no significant differences except less vitality in female carriers ($P=0.039$).

Twenty-three *SDH* mutation carriers (13 *SDHB* and 10 *SDHD* mutation carriers) were asymptomatic, i.e. had not displayed manifest disease up to the present. When analyzing this group separately, no significant differences in QoL scores were found compared with self-provided controls and age-adjusted reference values (21, 22, 23). *Post hoc* power calculations revealed sufficient power (>0.8) to draw these conclusions.

Factors influencing QoL in patients with paragangliomas

Age The SF-36 subscale physical functioning was negatively affected by age in the patient group ($\beta=-0.377$, $P=0.000$). None of the other variables were affected by age.

Gender Female paraganglioma patients experienced significantly more general fatigue than male patients (12.1 ± 4.6 vs 10.0 ± 4.8) and a significantly reduced motivation (9.7 ± 3.9 vs 8.5 ± 4.0). On the SF-36, females reported less vitality than males (57.6 ± 19.6 vs 65.9 ± 20.1, $P=0.008$).

HNPGLs There was no difference in QoL between patients with HNPGLs and patients without HNPGLs on all 16 dimensions. Surgical removal of HNPGLs was also not related to QoL scores. *Post hoc* power calculations yielded enough power (>0.8) to draw these conclusions.

A higher number of HNPGLs positively affected the HADS subscale depression ($\beta=0.489$, $P=0.030$),

Table 3 QoL parameters: patients with HNPGL *in situ* with associated complaints vs patients with HNPGL *in situ* without any complaints.

Questionnaire	Complaints ($n=108$)	No complaints ($n=18$)	*P* value
HADS			
Anxiety	6.5 ± 3.8	3.9 ± 2.5	<0.05
Depression	4.5 ± 3.9	2.1 ± 2.6	<0.05
Total	11.0 ± 6.9	6.0 ± 4.4	<0.05
MFI-20			
General fatigue	12.4 ± 4.7	7.7 ± 3.7	<0.001
Physical fatigue	10.9 ± 4.8	6.9 ± 2.8	<0.001
Reduced activity	9.6 ± 4.2	7.8 ± 2.9	NS
Reduced motivation	9.7 ± 4.1	8.1 ± 3.2	NS
Mental fatigue	10.4 ± 4.3	7.2 ± 4.1	<0.05
SF-36			
Physical functioning	80.7 ± 19.5	92.9 ± 9.2	<0.05
Social functioning	73.3 ± 25.9	93.1 ± 13.0	<0.05
Role limitations due to physical problems	64.4 ± 42.3	81.9 ± 30.7	NS
Role limitations due to emotional problems	75.9 ± 38.6	92.6 ± 21.6	NS
Mental health	69.8 ± 18.2	82.0 ± 10.8	<0.05
Vitality	56.9 ± 20.4	73.9 ± 11.8	<0.001
Bodily pain	80.7 ± 21.8	91.6 ± 14.6	<0.05
General health perception	56.1 ± 22.8	81.4 ± 12.5	<0.001
Health change	49.2 ± 19.9	58.3 ± 19.2	NS

NS, not significant; HADS, Hospital Anxiety and Depression Scale; MFI-20, Multidimensional Fatigue Index; SF-36, Short Form 36.

Table 4 QoL at baseline compared with QoL 5 years later in 41 patients.

Questionnaire	Patients at baseline	Patients at 5 years	*P* value
HADS			
Anxiety	5.7±3.7	6.7±4.4	0.167
Depression	3.5±3.4	4.1±4.4	0.359
Total	9.2±6.6	10.8±8.1	0.210
MFI-20			
General fatigue	10.6±5.2	11.6±4.9	0.117
Physical fatigue	9.6±4.3	10.1±4.8	0.480
Reduced activity	8.1±3.6	9.6±4.1	0.005
Reduced motivation	8.2±3.5	9.2±4.2	0.104
Mental fatigue	10.3±4.5	10.1±4.4	0.810

HADS, Hospital Anxiety and Depression Scale; MFI-20, Multidimensional Fatigue Index.

indicating that a higher number of HNPGLs is associated with more feelings of depression. Furthermore, a higher number of HNPGLs had a negative effect on physical functioning ($\beta = -2.445$, $P = 0.035$) and general health perception ($\beta = -3.834$, $P = 0.006$). Patients reporting HNPGL-associated complaints (e.g. tinnitus, dysphonia, and aspiration) reported a significantly worse QoL than HNPGL patients without complaints (Table 3). When analyzing this latter group separately, no decreased QoL was found compared with self-provided controls and age-adjusted reference values (21, 22, 23). *Post hoc* power calculation revealed sufficient power (>0.8) to detect differences between groups.

Pheochromocytomas and extra-adrenal paragangliomas The patient group with pheochromocytomas or extra-adrenal paragangliomas *in situ* was of insufficient size for separate analysis. Patients with a history of surgically treated pheochromocytomas or extra-adrenal paragangliomas were not found to have an altered QoL compared with the rest of the patient group (*post hoc* analysis power of >0.8).

Patients experiencing complaints associated with excessive production of catecholamines (i.e. vertigo, palpitations, perspiration, pallor, panic attacks, and headaches) did have significantly increased scores on the HADS and MFI-20 and impaired scores on SF-36 on more than eight out of 16 subscales.

Malignancy Patients with malignant paraganglioma reported significantly more mental fatigue (13.8±2.4 vs 9.9±4.3) and had a reduced score on the general health perception subscale (35.8±21.8 vs 63.6±22.5). All other subscales were not affected.

Long-term QoL

We were able to compare present QoL scores with those of 5 years ago on the HADS and MFI-20 in 41 patients. Results are displayed in Table 4. Patients reported a significantly increased score on the MFI-20 subscale relating to reduced activity. No significant alterations were found on the other subscales.

Seven patients (17%) were operated on their HNPGLs in these 5 years. It concerned four carotid body tumors, two jugulotympanic tumors, and one tumor localized in between the thyroid gland and right internal jugular vein. In addition, in one patient, an extra-adrenal paraganglioma was surgically removed. In none of these patients, postoperative morbidity was noted.

There were no significant differences in alteration of QoL between patients who were operated on and patients who were conservatively treated, although *post hoc* power calculation revealed insufficient power (0.5) to detect differences between groups.

Discussion

In this study, we assessed QoL in an extended cohort of paraganglioma patients and compared QoL in the various *SDH* mutation groups. Our study compared patients with 'own controls' as well as with age-adjusted literature values. The advantage of using own controls is the same distribution of sex, age, and geographical area in the control group as in the patient group (27). However, a potential problem of these controls is positive selection bias, i.e. the tendency of patients to choose controls with a good health status (28). Therefore, in addition to own controls, we used age-adjusted literary values that are not subject to this bias. The use of two control groups produces more reliable results if outcomes are consistent (27). Our study showed similar results for patients compared with own controls and compared with reference values derived from the literature.

Our results show that the study cohort as a whole had a significantly decreased QoL relating to fatigue and physical condition compared with own controls. Compared with age-adjusted literature values, patients were found to have decreased QoL scores on physical as well as psychological and social subscales. These results are in line with a previous study conducted in our department (13); however, in this study, the cohort was extended and included *SDHB* and *SDHC* mutation carriers.

When we attempt to put our results in perspective and compare the whole study group to patients with a similar condition, i.e. vestibular schwannoma, a similar benign tumor in the head-and-neck area primarily leading to hearing loss, paraganglioma patients seem to have less impairment of QoL on SF-36 scores (29). Comparing our results with other patients suffering from a chronic disease, i.e. diabetes type 2 patients, paraganglioma patients had similar QoL scores on the SF-36, except for better physical functioning and less bodily pain (30).

Assessment of determinants influencing QoL revealed that age negatively influenced physical functioning on the SF-36 subscale. This is not surprising, as it is known

that scores on all subscales of the SF-36 decrease with increasing age (23). More importantly, the presence of HNPGL-associated complaints significantly reduced QoL. Interestingly, HNPGL patients without associated complaints were not found to have a decreased QoL compared with the general population (i.e. own controls and values derived from the literature). Apparently, it is not the presence of a HNPGL *per se* that causes a decreased QoL but it is the associated signs and symptoms that do.

In our study, we aimed to explore potential differences in QoL between *SDHB*, *SDHC*, and *SDHD* mutation carriers and patients without an *SDH* mutation. Owing to the limited number of patients harboring an *SDHC* mutation in our cohort, we were not able to analyze these patients separately. However, no differences in QoL between the various *SDH* mutation carriers were found, reducing the potential weakness in our study of the very low number of patients with *SDHC* mutations.

Equal scores in QoL between the various *SDH* mutation carriers are rather remarkable because it is known that patients harboring an *SDHB* mutation are at increased risk for developing malignant paragangliomas (11, 12). To make *SDHB* mutation carriers aware of this risk, in our medical center, this is highlighted in a consult and a patient letter. One possible explanation for equal scores in QoL could be that a large proportion of *SDHB* mutation carriers in our cohort are asymptomatic, which is probably due to the reduced penetrance of the *SDHB* mutation in our cohort (31). A separate analysis of the group of asymptomatic mutation carriers showed that they do not display an alteration in QoL compared with the general population. These results are in concordance with results of studies exploring psychological well-being after presymptomatic genetic testing in other diseases, e.g. in mutation carriers of the gene predisposing for Huntington's disease and of spinocerebellar ataxia (32, 33). Apparently, mutation carriers of several genetic diseases display psychological resilience after receiving a positive test result for a genetic test.

Furthermore, as a consequence of the reduced penetrance, *SDHB* mutation carriers in our cohort are being confronted with severely affected family members to a lesser extent. Consequently, *SDHB* mutation carriers may worry less about developing (malignant) paragangliomas, as the experiences of other family members can be modifiers of how mutation carriers conceptualize their own risk (34). Interestingly, also no differences in QoL scores were found between female and male *SDHD* mutation carriers, the latter at risk to transmit the disease. In future research, it would be of interest to investigate how *SDH* mutation carriers conceptualize beliefs and representations about their disease, i.e. illness perceptions, and how they try to deal with it, i.e. coping strategies, as these determinants may affect QoL (35, 36).

We assessed long-term QoL in paraganglioma patients by comparing present results of patients with QoL scores they reported 5 years earlier. QoL is stable over time in paraganglioma patients, with the exception of patients reporting a reduced level of activity on the MFI-20. This latter might be due to older age; age-associated increases in mean scores in reduced activity have been reported earlier (37).

Our results imply that the generally applied 'wait and scan' policy does not negatively impact QoL over time, which is in concordance with QoL results in conservative treatment for vestibular schwannomas (38). This is very important information for both clinicians and paraganglioma patients when discussing different treatment options.

Although our power may have been limited by the small sample size, surgical management of paragangliomas did not seem to influence alteration in QoL. The fact that QoL did not decrease may partly be explained by the fact that none of the patients experienced postoperative morbidity; however, interestingly, surgical removal of paragangliomas did not increase QoL either. Two studies previously assessed postoperative QoL in paraganglioma patients. Kollert *et al.* (39) found no difference in depressive feelings of patients after HNPGL surgery compared with those of the general population. Briner *et al.* (40) reported that 75% of patients regained their preoperative QoL 1–2 years after surgery, but this information was self-reported by patients and not assessed by validated questionnaires. Both studies did not assess QoL preoperatively. We are the first to compare QoL scores in paraganglioma patients at two different moments in time. However, prospective, comparative research is needed to confirm our assumptions.

A potential limitation of our study may be the possibility of non-response bias influencing our results, as 42% of the 302 addressed patients did not return the questionnaires. However, the significance of this potential bias is unclear. Possibly, the most distressed persons were more likely to respond, which could have overestimated our results. On the other hand, people who are mentally or physically unwell might be less likely to participate, which could have led to an underestimation of our results. Nonetheless, besides a significantly higher percentage of women in the responder group, no significant difference in age, number, and localization of paragangliomas was found between responders and non-responders. Moreover, the differences in QoL between paraganglioma patients and control groups were very large, clearly indicating that the presence of symptomatic paragangliomas negatively influences QoL and general well-being.

In conclusion, our study confirms previous research stating QoL is decreased in paraganglioma patients but demonstrates that it is stable when measured over time. The impairment in QoL is significantly associated with the presence of HNPGL-associated complaints.

A difference in QoL between the various *SDH* mutation carriers was not found.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

L T van Hulsteijn was involved in the conception and design of the study, the acquisition, analysis, and interpretation of data, drafted the submitted manuscript, and approved the final version to be published. A Louisse was involved in the acquisition, analysis, and interpretation of data, drafted the submitted manuscript, and approved the final version to be published. B Havekes was involved in the design of the study, revised the manuscript critically, and approved the final version to be published. A A Kaptein and J W A Smit were involved in the conception and design of the study, the interpretation of data, revised the manuscript critically, and approved the final version to be published. J C Jansen was involved in the interpretation of data, revised the manuscript critically, and approved the final version to be published. F J Hes revised the manuscript critically and approved the final version to be published. E P M Corssmit was involved in the conception and design of the study, the analysis, and interpretation of data, drafted the submitted manuscript, and approved the final version to be published.

References

1 Pacak K. Preoperative management of the pheochromocytoma patient. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 4069–4079. (doi:10.1210/jc.2007-1720)

2 Gjuric M, Rudiger WS, Wigand ME & Weidenbecher M. Cranial nerve and hearing function after combined-approach surgery for glomus jugulare tumors. *Annals of Otology, Rhinology, and Laryngology* 1996 **105** 949–954.

3 Sajid MS, Hamilton G & Baker DM. A multicenter review of carotid body tumour management. *European Journal of Vascular and Endovascular Surgery* 2007 **34** 127–130. (doi:10.1016/j.ejvs.2007.01.015)

4 Jansen JC, van den Berg R, Kuiper A, van der Mey AG, Zwinderman AH & Cornelisse CJ. Estimation of growth rate in patients with head and neck paragangliomas influences the treatment proposal. *Cancer* 2000 **88** 2811–2816. (doi:10.1002/1097-0142(20000615)88:12<2811::AID-CNCR21>3.0.CO;2-7)

5 Astuti D, Latif F, Dallol A, Dahia PL, Douglas F, George E, Skoldberg F, Husebye ES, Eng C & Maher ER. Gene mutations in the succinate dehydrogenase subunit SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma. *American Journal of Human Genetics* 2001 **69** 49–54. (doi:10.1086/321282)

6 Baysal BE, Ferrell RE, Willett-Brozick JE, Lawrence EC, Myssiorek D, Bosch A, van der Mey A, Taschner PE, Rubinstein WS, Myers EN *et al*. Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. *Science* 2000 **287** 848–851. (doi:10.1126/science.287.5454.848)

7 Burnichon N, Briere JJ, Libe R, Vescovo L, Riviere J, Tissier F, Jouanno E, Jeunemaitre X, Benit P, Tzagoloff A *et al*. SDHA is a tumor suppressor gene causing paraganglioma. *Human Molecular Genetics* 2010 **19** 3011–3020. (doi:10.1093/hmg/ddq206)

8 Kunst HP, Rutten MH, de Monnink JP, Hoefsloot LH, Timmers HJ, Marres HA, Jansen JC, Kremer H, Bayley JP & Cremers CW. SDHAF2 (PGL2–SDH5) and hereditary head and neck paraganglioma. *Clinical Cancer Research* 2011 **17** 247–254. (doi:10.1158/1078-0432.CCR-10-0420)

9 Niemann S & Muller U. Mutations in SDHC cause autosomal dominant paraganglioma, type 3. *Nature Genetics* 2000 **26** 268–270. (doi:10.1038/81551)

10 Hensen EF, Siemers MD, Jansen JC, Corssmit EP, Romijn JA, Tops CM, van der Mey AG, Devilee P, Cornelisse CJ, Bayley JP *et al*. Mutations in SDHD are the major determinants of the clinical characteristics of Dutch head and neck paraganglioma patients. *Clinical Endocrinology* 2011 **75** 650–655. (doi:10.1111/j.1365-2265.2011.04097.x)

11 Benn DE, Gimenez-Roqueplo AP, Reilly JR, Bertherat J, Burgess J, Byth K, Croxson M, Dahia PL, Elston M, Gimm O *et al*. Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 827–836. (doi:10.1210/jc.2005-1862)

12 Neumann HP, Pawlu C, Peczkowska M, Bausch B, McWhinney SR, Muresan M, Buchta M, Franke G, Klisch J, Bley TA *et al*. Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. *Journal of the American Medical Association* 2004 **292** 943–951. (doi:10.1001/jama.292.8.943)

13 Havekes B, van der Klaauw AA, Hoftijzer HC, Jansen JC, van der Mey AG, Vriends AH, Smit JW, Romijn JA & Corssmit EP. Reduced quality of life in patients with head-and-neck paragangliomas. *European Journal of Endocrinology* 2008 **158** 247–253. (doi:10.1530/EJE-07-0464)

14 Filipsson NH, Barbosa EJ, Nilsson AG, Norrman LL, Ragnarsson O & Johannsson G. Discontinuing long-term GH replacement therapy – a randomized, placebo-controlled crossover trial in adult GH deficiency. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 3185–3195. (doi:10.1210/jc.2012-2006)

15 McGee H & Ring L. Quality of life. In *Health Psychology*, edn 2nd, pp 331–333. Eds D French, K Vedhara, AA Kaptein & J Weinman, Chichester: Blackwell Publishing Ltd., 2010.

16 Wilson IB & Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *Journal of the American Medical Association* 1995 **273** 59–65. (doi:10.1001/jama.1995.03520250075037)

17 Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T & Westlake L. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992 **305** 160–164. (doi:10.1136/bmj.305.6846.160)

18 Smets EM, Garssen B, Bonke B & De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *Journal of Psychosomatic Research* 1995 **39** 315–325. (doi:10.1016/0022-3999(94)00125-O)

19 Ware JE Jr & Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* 1992 **30** 473–483. (doi:10.1097/00005650-199206000-00002)

20 Zigmond AS & Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica* 1983 **67** 361–370. (doi:10.1111/j.1600-0447.1983.tb09716.x)

21 Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE & Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychological Medicine* 1997 **27** 363–370. (doi:10.1017/S0033291796004382)

22 Smets EM, Visser MR, Willems-Groot AF, Garssen B, Schuster-Uitterhoeve AL & De Haes JC. Fatigue and radiotherapy: (B) experience in patients 9 months following treatment. *British Journal of Cancer* 1998 **78** 907–912. (doi:10.1038/bjc.1998.600)

23 van der Zee KI & Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36, een handleiding. Groningen, The Netherlands: Noordelijk Centrum voor Gezondheidsvraagstukken, 1996.

24 Peyre H, Leplege A & Coste J. Missing data methods for dealing with missing items in quality of life questionnaires. A comparison

by simulation of personal mean score, full information maximum likelihood, multiple imputation, and hot deck techniques applied to the SF-36 in the French 2003 decennial health survey. *Quality of Life Research* 2011 **20** 287–300. (doi:10.1007/s11136-010-9740-3)

25 Biermasz NR, van Thiel SW, Pereira AM, Hoftijzer HC, van Hemert AM, Smit JW, Romijn JA & Roelfsema F. Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 5369–5376. (doi:10.1210/jc.2004-0669)

26 Faul F, Erdfelder E, Lang AG & Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods* 2007 **39** 175–191. (doi:10.3758/BF03193146)

27 Grimes DA & Schulz KF. Compared to what? Finding controls for case–control studies. *Lancet* 2005 **365** 1429–1433. (doi:10.1016/S0140-6736(05)66379-9)

28 Wacholder S, Silverman DT, McLaughlin JK & Mandel JS. Selection of controls in case–control studies. II. Types of controls. *American Journal of Epidemiology* 1992 **135** 1029–1041.

29 Vogel JJ, Godefroy WP, van der Mey AG, le Cessie S & Kaptein AA. Illness perceptions, coping, and quality of life in vestibular schwannoma patients at diagnosis. *Otology & Neurotology* 2008 **29** 839–845. (doi:10.1097/MAO.0b013e3181820246)

30 Luyster FS & Dunbar-Jacob J. Sleep quality and quality of life in adults with type 2 diabetes. *Diabetes Educator* 2011 **37** 347–355. (doi:10.1177/0145721711400663)

31 Hes FJ, Weiss MM, Woortman SA, de Miranda NF, van Bunderen PA, Bonsing BA, Stokkel MP, Morreau H, Romijn JA, Jansen JC *et al*. Low penetrance of a SDHB mutation in a large Dutch paraganglioma family. *BMC Medical Genetics* 2010 **11** 92. (doi:10.1186/1471-2350-11-92)

32 Duisterhof M, Trijsburg RW, Niermeijer MF, Roos RA & Tibben A. Psychological studies in Huntington's disease: making up the balance. *Journal of Medical Genetics* 2001 **38** 852–861. (doi:10.1136/jmg.38.12.852)

33 Paneque HM, Prieto AL, Reynaldo RR, Cruz MT, Santos FN, Almaguer ML, Velazquez PL & Heredero BL. Psychological aspects of presymptomatic diagnosis of spinocerebellar ataxia type 2 in Cuba. *Community Genetics* 2007 **10** 132–139. (doi:10.1159/000101754)

34 Hoskins LM, Roy KM & Greene MH. Toward a new understanding of risk perception among young female BRCA1/2 "previvors". *Families, Systems & Health: the Journal of Collaborative Family Healthcare* 2012 **30** 32–46. (doi:10.1037/a0027276)

35 Fan SY, Eiser C, Ho MC & Lin CY. Health-related quality of life in patients with hepatocellular carcinoma: the mediation effects of illness perceptions and coping. *Psychooncology* 2013. In press. (doi:10.1002/pon.3146)

36 Tiemensma J, Kaptein AA, Pereira AM, Smit JW, Romijn JA & Biermasz NR. Affected illness perceptions and the association with impaired quality of life in patients with long-term remission of acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 3550–3558. (doi:10.1210/jc.2011-1645)

37 Lin JM, Brimmer DJ, Maloney EM, Nyarko E, Belue R & Reeves WC. Further validation of the Multidimensional Fatigue Inventory in a US adult population sample. *Population Health Metrics* 2009 **7** 18. (doi:10.1186/1478-7954-7-18)

38 Godefroy WP, Kaptein AA, Vogel JJ & van der Mey AG. Conservative treatment of vestibular schwannoma: a follow-up study on clinical and quality-of-life outcome. *Otology & Neurotology* 2009 **30** 968–974. (doi:10.1097/MAO.0b013e3181b4e3c9)

39 Kollert M, Minovi A, Mangold R, Hendus J, Draf W & Bockmuhl U. Paraganglioma of the head and neck – tumor control, functional results and quality of life. *Laryngo-Rhino-Otologie* 2006 **85** 649–656. (doi:10.1055/s-2006-925234)

40 Briner HR, Linder TE, Pauw B & Fisch U. Long-term results of surgery for temporal bone paragangliomas. *Laryngoscope* 1999 **109** 577–583. (doi:10.1097/00005537-199904000-00011)

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