CLINICAL STUDY

Hemodynamic instability during resection of pheochromocytoma in MEN versus non-MEN patients

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Abstract

Objective: Hemodynamic (HD) instability still underlies difficulties during pheochromocytoma resection. Little is known about HD instability in patients with multiple endocrine neoplasia (MEN) type 2-related pheochromocytoma. Our aim was to assess differences in HD during pheochromocytoma resection between MEN2 and non-MEN patients. In addition, we sought to identify risk factors for intraoperative HD instability.

Design: Retrospective cohort study.

Methods: A total of 22 MEN2 and 34 non-MEN patients underwent 61 pheochromocytoma resections at the University Medical Center Utrecht between 2000 and 2010. All MEN2-related pheochromocytomas were diagnosed by annual screening. HD instability was assessed by measuring the frequency of hypotensive (mean arterial blood pressure (MABP) <60 mmHg) and/or hypertensive (systolic arterial blood pressure (SABP) >200 mmHg) episodes.

Results: Compared with non-MEN patients, MEN2 patients were younger at diagnosis, had less symptoms, lower hormone levels, and smaller tumors. Intraoperatively, MEN2 patients had a similar frequency of hypertensive episodes (1.3 vs 1.9, $P=0.162$, 95% confidence interval (CI): -6.7 to 35.4) and a similar maximum SABP (200 vs 220 mmHg, $P=0.180$, 95% CI: -9.7 to 50.5). However, MEN2 patients experienced less frequent (1.04 vs 2.6, $P=0.003$, 95% CI: 0.57 to 2.6) and less severe hypotensive episodes after tumor resection (lowest MABP: 52.5 vs 45.6 mmHg, $P=0.015$, 95% CI: -12.6 to 1.16). Tumor size was an independent risk factor for HD instability for the total group after multivariate analysis.

Conclusion: MEN2 patients with pheochromocytoma, despite their smaller tumors, do not distinguish themselves from non-MEN patients in terms of hypertensive episodes during pheochromocytoma resection. Therefore, pretreatment with α - and β -blockade remains the standard of care in MEN2-related as well as in non-MEN-related pheochromocytomas.

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Introduction

Pheochromocytomas are rare neuroendocrine catecholamine-secreting tumors, occurring mainly in the adrenal medulla (1, 2). Pheochromocytomas can occur as part of a familial syndrome and are, in that case, often diagnosed by periodic screening of known mutation carriers. Pheochromocytomas can present with symptoms or as an incidental mass on radiological imaging studies. Symptoms include episodic hypertension, headaches, and palpitations. Hypertensive crisis may develop in some patients that can result in myocardial infarction, cerebral vascular accident, renal failure, acute respiratory distress syndrome, and/or mortality (3).

Surgical resection is the treatment of choice for pheochromocytoma, although the surgical procedure itself can be life threatening due to hypertensive crises

and multiorgan failure or profound hypotension after tumor resection (4, 5). During induction of anesthesia or surgical manipulation of their tumors, patients with pheochromocytoma may have wide swings in blood pressure (BP) and heart rate (HR) (6). Administration of α -, β -, and/or calcium channel blockers is assumed to lower the risk of intraoperative hemodynamic (HD) instability (including preventing a hypertensive crisis), although randomized, controlled trials are lacking (2, 7, 8).

Preoperative medication and improvements in surgical and anesthetic techniques have nearly diminished the risk of perioperative mortality associated with pheochromocytoma resection (3, 6). However, intraoperative HD fluctuations can lead to serious morbidity (9). Recently, high plasma norepinephrine concentration, tumor size larger than 4 cm, a high mean arterial BP (MABP) at presentation and after α -blockade, and more profound

postural BP reduced after α -blockade were identified as risk factors for HD instability during pheochromocytoma resection (10).

Literature on perioperative care of patients undergoing adrenalectomy for pheochromocytoma is often outdated and historical without considering the improvements in perianesthetic care mentioned earlier (11). Moreover, the perioperative course concerning HD data of multiple endocrine neoplasia type 2 (MEN2) patients with pheochromocytomas has typically been reported only in conjunction with sporadic cases and patients with other familial syndromes or has included only small numbers of patients (7, 12–14).

Because of their early identification using the annual screening of mutation carriers, we questioned whether MEN2-related pheochromocytomas are associated with less HD instability during pheochromocytoma resection. Therefore, we assessed differences in intraoperative HD between MEN2 and non-MEN patients in a large cohort. In addition, we sought to identify risk factors for intraoperative HD instability.

Subjects and methods

We took the opportunity of a large database of patients for pheochromocytoma resection, at the University Medical Center Utrecht (UMCU) in The Netherlands from January 2000 to August 2010 following a homogeneous anesthetic and surgical care, to investigate whether patients with MEN have different intraoperative HD compared with non-MEN patients. A total of 56 patients were considered for this investigation after selection from the pathology database in which the pathology results of all operatively removed tissues are included.

In our institution, the diagnosis of pheochromocytoma is based on the urinary laboratory results of catecholamines and metanephrines and the presence of an (extra-)adrenal tumor on imaging. MEN2 is defined as the presence of an MEN2 mutation in the *RET* gene. All pheochromocytomas in MEN2 patients were diagnosed using (annual, biochemical) screening.

α -Blockers (doxazosin) are administered to all patients at least 2 weeks before operation. β -Blockers (metoprolol) are administered to a subgroup of patients with a HR above 80 beats/min after adequate α -blockade. Patients are encouraged to hydrate themselves well and a salty diet is advised. Patients are admitted 1 week before surgery to maximize the dose of doxazosin and to start saline infusion 2 days before surgery. Criteria for efficacy include a systolic arterial BP (SABP) below 140–160 mmHg and a HR below 80 beats/min. Anesthetic care includes propofol, rocuronium, sufentanil and/or isoflurane, or enflurane. Intraoperatively, BP and HR values are automatically, continuously, and digitally recorded by invasive measurement through an arterial line in the radial artery. Central venous pressure is measured in all

patients. Undesirable elevations in BP or HR during surgery are treated with i.v. doses of nitrates, phentolamine, and/or esmolol. Crystalloids or colloids are infused and (nor)epinephrine, phenylephrine, and/or ephedrine are administered in case of hypotension after tumor removal.

Variables investigated included patient demographics, urinary hormone levels, tumor size on preoperative imaging (computed tomography (CT) or magnetic resonance imaging (MRI)), and preoperative blockade regimes. The outcomes of hormone level were adjusted by generating a ratio of the highest level for that hormone divided by the corresponding upper limit of normal. In addition, maximum and minimum SABP, diastolic arterial BP (DABP) and MABP, and HR throughout surgery were studied. The MABP was calculated by dividing the sum of the SABP and two times the DABP by three. To measure HD fluctuations, the number of episodes that the SABP was above 200 mmHg, chosen as cutoff value for intraoperative hypertension, was scored. In addition, hypotensive complications were measured according to the number of episodes that the MABP was below 60 mmHg. Intraoperative tachycardia and bradycardia were defined as an HR above 100 and below 45 beats/min respectively.

Statistical analysis

MEN2 patients were compared with the non-MEN patients regarding patients' demographics, disease- and treatment-related features, and regarding differences in outcome of HD instability. In addition, patients' demographics, urinary catecholamine levels, and tumor size, among other variables, were correlated with intraoperative BP fluctuations.

All data were analyzed with SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA). Independent samples *t*-test was used for comparisons between groups. Pearson's correlation coefficient was used to correlate variables (*r* value). Multivariate linear regression analysis was used to adjust for confounding factors. Statistical significance was shown at $P < 0.05$.

Results

Between January 2000 and August 2010, total of 56 patients underwent 61 resections for pheochromocytoma. Almost all patients ($n = 52$) were operated by the same surgeon (I B R). Among those, five patients underwent bilateral adrenalectomy because of bilateral pheochromocytoma. Our study population consisted of 39% MEN2 patients.

MEN versus non-MEN

Patient and tumor/diagnostic characteristics for the MEN2 group versus the non-MEN group are shown in

Table 1 Characteristics of MEN vs non-MEN patients

	MEN	Non-MEN	P value (95% CI)
Patient characteristics			
Patients, <i>n</i> (% of total population)	22 (39)	34 (61)	
Classification, <i>n</i>	21 MEN2A, 1 MEN2B	26 Sporadic, 3 VHL, 3 SDHD, 2 Neurofibromatosis	
Age at surgery (years, mean $\pm$ s.d.)	34 $\pm$ 12.1	46 $\pm$ 14.3	0.001 (4.74 to 19.74)
Female, <i>n</i> (%)	8 (36.6)	17 (50)	0.344 (−0.40 to 0.16)
ASA physical status (mean $\pm$ s.d.)	2.10 $\pm$ 0.3	2.26 $\pm$ 0.5	0.128 (−0.50 to 0.39)
Co-morbidity, <i>n</i>			
History of cardiovascular disease	3	13	0.140 (−0.25 to 0.45)
Respiratory disease (pneumonia, COPD)	0	4	0.444 (−0.43 to 0.56)
Endocrine disease (diabetes mellitus)	0	4	0.444 (−0.43 to 0.56)
Tumor and diagnostic characteristics			
Bilateral localization, <i>n</i>	4	3	0.32 (−0.31 to 0.10)
Hypertension at diagnosis, <i>n</i>	6	22	0.009 (0.09 to 0.63)
Clinical manifestations, <i>n</i>	9	23	<0.000 (−1.23 to −0.40)
Manifestations per patient, <i>n</i> (mean $\pm$ s.d.)	2.7 $\pm$ 2.5	3.9 $\pm$ 2.2	0.065 (−0.08 to 2.54)
Cardiac manifestations, <i>n</i>	2	13	0.010 (0.07 to 0.50)
Highest urinary hormone ratio (multiplication of reference value, mean $\pm$ s.d.)	4.5	18.1	0.001 (5.91 to 21.32)
Metanephrine	3.4 $\pm$ 3.0	9.4 $\pm$ 20.1	0.102 (−1.25 to 13.22)
Normetanephrine	2.7 $\pm$ 2.9	9.7 $\pm$ 9.9	0.001 (3.08 to 10.98) ^a
Epinephrine	3.9 $\pm$ 4.2	6.8 $\pm$ 11.9	0.200 (−1.60 to 7.46)
Norepinephrine	1.2 $\pm$ 1.6	6.9 $\pm$ 7.1	<0.000 (3.08 to 8.24) ^b
Largest tumor diameter on imaging (cm), mean $\pm$ s.d. (range)	2.6 $\pm$ 1.7 (1.0 to 7.7)	5.2 $\pm$ 2.6 (1.3 to 12.0)	<0.000 (13.51 to 36.62)
Time symptoms to diagnosis (days, mean $\pm$ s.d.)	56 $\pm$ 154	559 $\pm$ 952	0.007 (140.8 to 831.91)
Time symptoms to surgery (days, mean $\pm$ s.d.)	226 $\pm$ 162	651 $\pm$ 939	0.021 (65.5 to 749.51)
Time diagnosis to surgery (days, mean $\pm$ s.d.)	175 $\pm$ 117	92 $\pm$ 79	0.003 (−138.7 to −30.94)

MEN, multiple endocrine neoplasia; VHL, Von Hippel–Lindau syndrome; SDHD, mutation in succinate dehydrogenase B, C, and D; COPD, chronic obstructive pulmonary disease. Independent sample *t*-test was used for comparisons between groups.

Table 1. Significant differences between both groups included a younger mean age at diagnosis, less (cardiac) symptoms, lower preoperative urinary hormone levels, and a smaller tumor size on preoperative imaging for MEN2 patients.

Preoperative differences between MEN2 and non-MEN patients in terms of BP and HR (Table 2) were diminished after preoperative medication (Table 3). Anesthesia was comparable between both groups (data not shown). Intraoperatively, MEN2 patients were similar to non-MEN patients in terms of hypertension, i.e. the number of hypertensive episodes, the maximum SABP, and the number of interventions needed to treat undesirable elevations in SABP. In contrast, MEN2 patients experienced less frequent and less severe hypotensive episodes after tumor resection (Table 2). The differences between MEN2 and non-MEN patients did not change after exclusion of patients with Von Hippel–Lindau syndrome (VHL), mutation in succinate dehydrogenase B, C, and D (SDHD), or neurofibromatosis (data not shown).

There were no significant differences between the two groups regarding postoperative course (Table 4).

Correlations with tumor size

The average tumor size based on imaging studies for the total group was 4.2 cm (range 1–12 cm). We found a

correlation between tumor size and preoperative urinary hormone levels ($r=0.64$, $P<0.000$). There were weak correlations between tumor size and the number of (cardiac) symptoms and the presence of hypertension at diagnosis ($r=0.29$, $P=0.025$; $r=0.26$, $P=0.050$ respectively).

Correlations of tumor size and systolic BP were significant regarding highest SABP at tumor manipulation ($r=0.39$, $P=0.002$) and lowest SABP at tumor resection ($r=0.497$, $P<0.000$) and hypertensive ($r=0.50$, $P<0.000$) and hypotensive episodes ($r=0.60$, $P<0.000$). Tumor size also correlated with the number of interventions of the anesthesiologist, i.e. the frequency of using antihypertensive medications during tumor manipulation ($r=0.40$, $P=0.002$) and need for vasopressors after tumor resection ($r=0.66$, $P<0.000$). These correlations were also significant in multivariate analysis after adjustment for familial syndrome status, preoperative BP and HR, preoperative urinary hormone levels, pre-treatment regimes, and laparoscopic or open surgery.

The correlation with variables associated with arterial BP was strongest for tumors larger than 3 cm. A tumor diameter larger than 3 cm was accompanied by significantly more hypertensive and hypotensive episodes compared with a tumor diameter of 3 cm or less (2.02 vs 0.47, $P<0.000$; 2.51 vs 0.83, $P<0.000$

Table 2 MEN vs non-MEN patients: hemodynamic data.

	MEN	Non-MEN	P value (95% CI)
SABP ^a (mmHg, mean $\pm$ s.d.)			
At diagnosis	137 $\pm$ 22	157 $\pm$ 34	0.014 (4.1 to 35.2)
After preoperative medication	125 $\pm$ 16	126 $\pm$ 18	0.782 (–7.6 to 10.0)
Pre-start ^b	139 $\pm$ 20	146 $\pm$ 17	0.101 (–1.5 to 16.8)
After induction	93 $\pm$ 19	87 $\pm$ 20	0.287 (–15.5 to 4.7)
During tumor manipulation	191 $\pm$ 48	204 $\pm$ 62	0.382 (–17.7 to 42.8)
After tumor resection	94 $\pm$ 23	75 $\pm$ 23	0.001 (–31.5 to –8.1)
Intraoperative hypertension			
Hypertensive episodes (mean $\pm$ s.d.), <i>n</i>	1.3 $\pm$ 1.4	1.9 $\pm$ 2.0	0.162 (–6.7 to 35.4)
Maximum SABP (mmHg, mean $\pm$ s.d.)	200 $\pm$ 57	220 $\pm$ 55	0.180 (–9.7 to 50.5)
Interventions needed to treat undesirable elevations in SABP (mean $\pm$ s.d.), <i>n</i>	11.4 $\pm$ 9.1	14.8 $\pm$ 18.8	0.439 (–5.31 to 12.1)
Intraoperative hypotension			
Hypotensive episodes (mean $\pm$ s.d.), <i>n</i>	1.04 $\pm$ 1.2	2.6 $\pm$ 2.6	0.003 (0.57 to 2.6)
Minimum MABP (mmHg, mean $\pm$ s.d.)	52.5 $\pm$ 10	45.6 $\pm$ 12	0.015 (–12.6 to –1.16)
Interventions needed to treat undesirable decreases in MABP (mean $\pm$ s.d.), <i>n</i>	1.9 $\pm$ 3.8	5.1 $\pm$ 5.0	0.007 (0.9 to 5.6)

SABP, systolic arterial blood pressure; MABP, mean arterial blood pressure. Independent sample *t*-test was used for comparisons between groups.

^aSimilarities and differences between MEN and non-MEN patients can be found for diastolic arterial blood pressure and heart rate, with similar *P* values.

^bThe first systolic blood pressure measurement in the operation room.

respectively). A larger tumor led to more hypotensive episodes after tumor resection. Although the correlation between hypertensive episodes and tumors larger than 3 cm is high, small tumors can also lead to HD instability and especially to hypertension during surgery.

Discussion

Due to considerable improvements in preoperative medical preparation and perioperative anesthetic control, mortality after pheochromocytoma resection is rare. However, (morbidity from) intraoperative HD instability remains a problem. The perioperative HD course of MEN2 patients with a pheochromocytoma has typically been reported only in case reports (6, 10, 12, 14). We report results of a large cohort study comparing patients with MEN2-related pheochromocytoma with non-MEN patients with pheochromocytoma. We mainly demonstrated that MEN2 patients with pheochromocytoma do not distinguish themselves from sporadic cases of pheochromocytoma in terms of intraoperative

hypertensive episodes. In addition, we also report results on hypotension during pheochromocytoma resection, where others have only focused on rises in BP and hypertensive crisis. Importantly, reduced BP associated with reduced plasma catecholamine release after tumor resection is the major cause of death. Furthermore, we demonstrated that after multivariate analysis, tumor size is an independent risk factor for HD instability.

Clinically, pheochromocytoma in MEN2 patients differs from sporadic pheochromocytoma because they are often identified at an earlier stage because of annual screening of known mutation carriers. In most cases, earlier diagnosis leads to the identification of smaller tumors, often associated with fewer symptoms and less often and less severe hypertension. In our study, indeed 70% of the MEN2 patients were normotensive and only 43% had symptoms. Cardiovascular symptoms associated with pheochromocytoma occurred in two of our MEN2 patients. These results are in agreement with previous studies (12, 15).

However, despite preoperative differences between MEN2 and non-MEN patients, BP after preoperative medication and intraoperative HD instability in terms

Table 3 MEN vs non-MEN patients: (pre)operative treatment regimes.

	MEN	Non-MEN	P value (95% CI)
Duration of α -blockade (days), mean $\pm$ s.d. (<i>n</i>)	74 $\pm$ 50 (22)	48 $\pm$ 42 (33)	0.047 (–51.91 to –0.37)
Daily dosage doxazosin (mg), mean $\pm$ s.d. (<i>n</i>)	17 $\pm$ 12 (22)	24 $\pm$ 20 (31)	0.048 (0.11 to 20.43)
Duration of β -blockade (days), mean $\pm$ s.d. (<i>n</i>)	115 $\pm$ 150 (10)	56 $\pm$ 97 (16)	0.269 (–164.8 to 48.12)
Additional antihypertensive, <i>n</i>	1	12	0.005 (0.09 to 0.47)
Preoperative saline infusion, <i>n</i>	11	20	0.647 (–0.22 to 0.35)
Preoperative admission days (mean $\pm$ s.d.)	3.5 $\pm$ 3.3	3.7 $\pm$ 3.4	0.833 (–1.68 to 2.10)
Laparoscopic surgery, <i>n</i>	20	17	0.004 (–0.59 to –0.12)

Independent sample *t*-test was used for comparisons between groups.

Table 4 MEN vs non-MEN patients: postoperative data.

	MEN, <i>n</i> =22	Non-MEN, <i>n</i> =34	<i>P</i> value (95% CI)
Postoperative admission days (mean $\pm$ s.d.)	4.8 $\pm$ 2.2	6.6 $\pm$ 4.7	0.136 (–0.46 to 3.30)
Total admission days (mean $\pm$ s.d.)	8.3 $\pm$ 3.8	10.3 $\pm$ 6.2	0.243 (–1.14 to 4.40)
IC admission days, mean $\pm$ s.d. (<i>n</i>)	1.4 $\pm$ 1.4 (7)	1.5 $\pm$ 1.7 (8)	0.437 (–1.52 to 1.63)
Postoperative complications, <i>n</i>			
Tension, heart rate or fluid related ^a	3	6	0.649 (–0.18 to 0.24)
Cerebrovascular events	0	0	–
Mortality	0	0	–
Other ^b	1	4	0.389 (–0.09 to 0.23)
Malignant pheochromocytoma, <i>n</i>	0	1	0.437 (–0.05 to 0.11)

Independent sample *t*-test was used for comparisons between groups.

^aIncluding hypertension during the first postoperative days requiring additional antihypertensive, direct postoperative hypotension requiring vasopressors (mainly norepinephrine) and intravascular fluid therapy, atrial fibrillation, pulmonary edema, and cardiac stunning (caused by relative cardiomyopathy secondary to the pheochromocytoma in combination with intraoperative fluid therapy).

^bIncluding wound infection, pneumonia, and intrauterine fetal death.

of rises in BP were similar in both groups. This might mean that the relatively small MEN2-related pheochromocytomas are easily provoked to secrete catecholamines during resection. In contrast with rises in BP, MEN2 patients experienced less frequent and less severe hypotensive episodes. These differences between groups were independent of doxazosin doses on the day of surgery.

Preoperative treatment in our study involved doxazosin in combination with metoprolol if indicated. In all of our patients, a mean SABP of 125 mmHg was obtained after blockade. Multivariate analysis in our study demonstrated that the titrated doses of doxazosin administered preoperatively was not related to SABP after tumor resection ($P=0.927$), indicating that in our patients higher α -blocker doses did not lead to a more profound decrease in BP after tumor removal. Bruynzeel *et al.* (10) and Prys-Roberts & Farndon (16) found similar results for doxazosin and phenoxybenzamine in terms of controlling arterial pressure and HR before and during surgery, but doxazosin caused fewer undesirable side effects both before and after surgery (16). Theoretically, patients with pheochromocytoma have a reduced intravascular volume owing to catecholamine-mediated vasoconstriction (17, 18). Patients in our study, therefore, received i.v. saline infusion therapy 2 days before surgery and a salty diet if they had tachycardia.

A recent report demonstrated a correlation between tumor size and HD instability (SABP above 160 mmHg) during pheochromocytoma resection (10), although others failed to demonstrate tumor size to be a risk factor (19, 20). The results of our study confirm that tumor size may be correlated with HD instability. However, we found a cutoff size of 3 cm instead of 4 cm (11) for significant association (SABP > 200 mmHg), independent of preoperative hormone levels, preoperative medication, surgical approach, and the presence of a familial syndrome. This correlation, as stated, is independent of surgical approach. However, surgical skill in handling the tumor can be a risk factor in intraoperative HD instability (19). In our study, almost all patients were operated by the same surgeon, which

makes surgical skill less likely to play a significant role in differences in intraoperative HD between patient groups.

Previous studies have demonstrated a direct relationship between tumor size and hormone levels in plasma and urine (21–23). Preoperative urinary hormone levels in our study also correlated with tumor size and to an extent intraoperative hypertension, as an independent risk factor for HD instability. The latter is also shown in the literature (12, 24). Our MEN2 patients had the highest urinary hormone ratio for epinephrine compared with (nor)metanephrine and norepinephrine. They also had significantly less norepinephrine secretion compared with our non-MEN patients. This is in agreement with previous studies (25, 26).

A limitation of our study is its retrospective design. Therefore, patients could not be randomized for different pretreatment regimes. However, our preoperative treatment protocol makes no distinction between familial cases of pheochromocytoma and sporadic cases. This is confirmed by the fact that dosage of α -blockade is not a confounder in identifying risk factors for HD instability. Because all HD data and use of medication during pheochromocytoma resection were recorded automatically, continuously, and digitally, only few data were missing. We used the hormone ratio to account for the differences in type of urinary hormone excreted in highest amount by the patient. Despite this, accurate correlation between tumor size and hormone level may still be affected. CT and MRI were used for preoperative imaging, which can result in size measurement variations. In addition, multiple radiologists interpreted the preoperative imaging scans, producing operator variation in final size determination.

Conclusion

Despite earlier diagnosis and significantly smaller tumors, MEN2 patients with pheochromocytoma do not distinguish themselves from sporadic cases of pheochromocytoma in terms of intraoperative hypertensive episodes. Therefore, pretreatment with α -blockade

started at least 2 weeks before surgery in combination with β -blockade, if tachycardia is present, remains important; MEN2 patients or patients with small tumors are not excluded.

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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