Interest of systematic screening of pheochromocytoma in patients with neurofibromatosis type 1

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Abstract

Objective: Pheochromocytoma (PHEO) may occur in 0.1–5.7% of patients presenting with a neurofibromatosis type 1 (NF1). Current recommendations are to explore only symptomatic patients. The objective of the study is to evaluate the prevalence and the interest of a systematic PHEO screening in this population.

Design: A prospective study in a French tertiary center including consecutive NF1 patients older than 18 years.

Methods: A systematic screening combining abdominal imaging and urinary fractionated metanephrines was proposed. In case of positivity of one or both exams, 123I-metaiodobenzylguanidine scintigraphy or [18F]-fluoro-dihydroxyphenylalanine PET imaging was performed. The diagnosis of secreting PHEO was retained in case of elevated urinary metanephrines associated with positive scintigraphy and non-secreting PHEO when urinary metanephrines were normal with a positive scintigraphy.

Results: Between January 2014 and August 2015, 234 patients were included and 156 patients (66.7%) completed both exams. In these 156 patients, 12 PHEOs were diagnosed, representing a prevalence of 7.7%. Of these, six PHEOs were secreting, with only two symptomatic patients. The tumor size of these PHEOs were bigger than that of non-secreting PHEO (25.2 ± 6.6 vs 14 ± 6.9 mm, P = 0.0165). One lesion was bilateral. Mean metanephrine and normetanephrine levels were 3.2 ± 2.6 N and 2.8 ± 1 N respectively. Three patients underwent surgery. The six patients with non-secreting PHEO were asymptomatic. One of them had bilateral lesion and one underwent surgery.

Conclusions: PHEO in NF1, whether or not secreting, are mostly asymptomatic. The current strategy to explore only symptomatic patients leads to an underestimation of prevalence with the risks inherent to the existence of an unrecognized PHEO.

Introduction

Neurofibromatosis type 1 (NF1), formerly named von Recklinghausen’s disease, is a common inherited disorder with a prevalence of one case in 3000 births irrespective of sex or ethnic origin (1, 2). NF1 is an autosomal dominant condition with complete penetrance but an extremely variable phenotype. The disease is caused by mutation in the NF1 gene (Ch 17), which is a classical tumor suppressor. The diagnosis is clinical with formal diagnostic criteria being published by the National Institutes of Health in 1987 (3) (Table 1). The main characteristic manifestations...
of NF1 are café au lait patches, neurofibromas (benign peripheral nerve sheath tumors), skin-fold freckling, iris Lisch nodules (hamartomas diagnosed on slit-lamp examination), and characteristic bony dysplasia of the long bones and sphenoid wing. Pheochromocytoma (PHEO), defined in 2004 by the World Health Organization as a tumor arising from adrenomedullary chromaffin cells that commonly produces one or more catecholamines (epinephrine, norepinephrine and dopamine) (4), is estimated to occur in 0.1–5.7% of patients with NF1 (5, 6). As it is a rare tumor, screening is not recommended in asymptomatic patients (7, 8). However, Zinnamosca et al. (9) in 2011 found a PHEO prevalence of 14% in a population of 48 consecutive NF1 patients, suggesting an underestimation of the prevalence of these lesions in this population. The objective of the study was to evaluate the prevalence and the interest of a systematic screening of PHEO in a NF1 population.

**Patients and methods**

**Patients**

This prospective single-center study including consecutive patients older than 18 years, consulting for NF1 since January 2014, was conducted in a regional competence center of NF1 (Centre Léon Bérard, Lyon, France). The study was performed according to French laws at the time of the initiation of the study and followed the principles laid down in the Declaration of Helsinki. Oral consent was obtained after a complete explanation of the protocol to the patients and was reported in the patient’s medical record. Written consent was not specifically needed, as it was waived by the Centre Léon Bérard IRB, which approved this prospective study.

NF1 diagnosis was confirmed when patients met two or more of the seven criteria according to NIH consensus criteria (3). Blood pressure measured on both arms and symptoms as headaches, flushing, weakness, sweating, heart palpitations, weight loss, depression, and back pain were reported. Hypertension was defined as increased systolic blood pressure and diastolic blood pressure above 140 and 90 mmHg respectively, or the use of antihypertension medication.

**Study design**

A systematic screening was suggested to patients, combining measurement of urinary fractionated metanephrines and imaging by abdominal computed tomography (CT) or abdominal ultrasound in non-overweight patients (BMI < 25 kg/m²) or in case of CT refusal. Plasma-free metanephrines was not measured due to the high cost of this procedure in a context of systematic screening. If ultrasound was abnormal or if both adrenal glands were not visible, a complementary abdominal CT was performed. In case of positivity of one or both exams, [123I]-metaiodobenzylguanidine (MIBG) scintigraphy or [18F]-fluorodeoxyxylfalanine ([18F]-FDOPA) PET-CT was performed.

Quantification of urinary fractionated metanephrines was realized by Biomnis laboratory (Lyon, France) by high-performance liquid chromatography (HPLC). Results were considered positive when the rate of metanephrine (MA) and/or normetanephrine (NMA) was equal to or greater than twice normal (2N): 1500 nmol/24 h for MA and 2200 nmol/24 h for NMA before 01/05/2015 and 228 nmol/24 h for MA and 213 nmol/24 h for NMA after 01/05/2015. 3-Ortho-methyldopamine was also quantified with a normal at 232 nmol/24 h and then at 320 nmol/24 h before and after 01/05/2015 respectively.

Abdominal ultrasound and CT were performed in various private radiology centers. Protocol of CT included sequences without and with contrast injection at arterial and portal time. When available, spontaneous density and contrast washout of the adrenal lesions were reported.

**Scintigraphy protocol**

The first patients included in the study underwent [123I]-MIBG scintigraphy and, as soon as [18F]-FDOPA
PET-CT became available, the PET-CT was preferred for the following reasons: higher resolution, no necessity of thyroid blockage and interruption of antihypertension medication, and 1-day procedure.

$^{123}$I-MIBG acquisitions were performed on Tandem Discovery NM/CT 670 from GE Healthcare Systems (Milwaukee, US) 24 h after injection of 370 MBq of iobenguane sulfate $i$-$123$ (AdreView, GE Healthcare, Medi-Physics, Inc, Arlington Heights, IL, USA). Planar 13.3 cm/min speed whole-body acquisition was followed by a SPECT/CT acquisition centered on the upper abdomen (60 frames, 15-s projections were acquired over 360°, 128×128 Matrix, MEGP/ PARA collimator grid, 40×54 cm FOV).

$[^{18}F]$-FDOPA PET-CT acquisition started 1 h after intravenous injection of 3 MBq/kg of $[^{18}\text{F}]$-DOPA (IASOdopa, from Advanced Accelerator Applications (AAA) France). No iodinated contrast material was administered. PET-CT was performed using the same protocol for every patient on a GEMINI TF 16 or TEP GEMINI TF16 BIG BORE (Philips Healthcare) from the top of the head to mid-thighs.

Criteria used for diagnosis of pheochromocytoma

The diagnosis of secreting PHEO was retained in case of elevated urinary metanephrines (MA and/or NMA $\geq 2N$) associated with positive scintigraphy, and non-secreting PHEO when urinary metanephrines were both normal with a positive scintigraphy.

Surgery and pathological examination

Patients with secreting PHEO underwent laparoscopic surgery in the University Hospital of Lyon Sud. Medical preparation included 15 days of calcium channel blockers (nicardipine 50 mg twice a day) and regimen rich in sodium. In per-operative period, blood pressure and heart rate were digitally recorded automatically and continuously via a catheter in the radial artery. Every attempt was made to clip-ligate the main adrenal vein early during laparoscopic adrenalectomy, before manipulating the adrenal tumor. Undesirable blood pressure elevations during surgery were treated with iv nicardipine. Undesirable heart rate elevations were treated with i.v. beta blockers. Immediately after tumor removal, glycemia monitoring was realized because of the risk of severe hypoglycemia. All patients were reexamined within 1 month post-operatively. Patients with only secreting PHEO and non-secreting PHEO with a tumor size higher than 2 cm underwent surgery. The others were followed every 6 months with urinary fractionated metanephrines and abdominal CT.

It is not possible to determine malignancy by histological evaluation. However, pathology criteria such as size, weight, presence of tumor necrosis, capsular invasion, Ki-67 index greater than 4%, and absence of PS100, which are linked to a greater risk of malignancy (10), were reported.

Statistical analysis

Data are given as mean±s.d. and median (range) and analyzed using unpaired Student’s $t$-test. Differences were considered statistically significant at $P<0.05$. Pearson’s correlation coefficient was applied to analyze the correlation between tumor size and metanephrine secretion in secreting PHEO.

Results

Between January 2014 and August 2015, 234 patients were included. Characteristics of patient population are presented in Table 2.

Overall, 156 patients completed the two exams, representing 66.7% of patients. Of these 156 patients, 12 PHEOs were diagnosed, giving a prevalence of 7.7%: six secreting PHEOs and six non-secreting PHEOs (Fig. 1).

Table 2  Characteristics of patient population.

<table>
<thead>
<tr>
<th></th>
<th>All patients $(n=234)$</th>
<th>Patients with full screening $(n=156)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (H/F)</td>
<td>98/136</td>
<td>75/81</td>
</tr>
<tr>
<td>Age (years)</td>
<td>mean±s.d. 41.3±14</td>
<td>43.9±14*</td>
</tr>
<tr>
<td></td>
<td>median (range) 38 (18–79)</td>
<td>42.5 (18–77)</td>
</tr>
<tr>
<td>Hypertension (n (%))</td>
<td>28 (12%)</td>
<td>21 (13.5%)</td>
</tr>
<tr>
<td>Urinary fractionated metanephrines</td>
<td>177</td>
<td>156</td>
</tr>
<tr>
<td>Abdominal imaging</td>
<td>CT 178</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td>Ultrasound 29</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Scintigraphy 23</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>$^{123}$I-MIBG 4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>$[^{18}\text{F}]$-FDOPA</td>
<td>19</td>
</tr>
</tbody>
</table>

$[^{18}\text{F}]$-FDOPA, $[^{18}\text{F}]$-fluoro-dihydroxyphenylalanine PET imaging; $^{123}$I-MIBG, $^{123}$I-metaiodobenzylguanidine scintigraphy; CT, computed tomography.

*P=0.06 for the comparison by unpaired Student’s $t$-test with all patients group.
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Patients with pheochromocytoma

Characteristics of patients with secreting and non-secreting PHEO are reported in Table 3.

Age at diagnosis was not different between both groups (55.3±13.7 for secreting PHEO vs 53.2±15.9 for non-secreting PHEO, P=0.805), but was significantly greater in patients with secreting PHEO than in screened patients with negative explorations (55.3±13.7 vs 43.1±13.9, P=0.036). The difference was not significant for non-secreting PHEO (53.2±15.9 vs 43.1±13.9, P=0.086).

Only two patients with secreting PHEO had symptoms at diagnosis: one underwent a treatment for hypertension with blood pressure up to 180/80 mmHg, which did not regress after surgery. The other patient had paroxysmal hypertension with headaches for the past few years, with blood pressure of 160/100 mmHg at annual visit.

Tumor size of secreting PHEO was significantly higher than that of non-secreting PHEO (25.2±6.6 vs 14±6.9 mm, P=0.0165) as well as NMA secretion (2.8±1 N vs 0.75±0.1 N, P=0.0008). However, no correlation was found between tumor size and metanephrine secretion in secreting PHEO (Fig. 2).

There were two bilateral PHEOs (16.6% of PHEO): one synchronous secreting PHEO (patient 1) and one metachronous non-secreting PHEO (patient 7) with a previous secreting PHEO treated by surgery in 1985. One patient with secreting PHEO (patient 3) had a contralateral adenoma (12 mm, spontaneous density 5UH, washout 66%).

Abnormal biology

Twelve (7.2%) patients presented an isolated elevation of urinary fractionated metanephrines without abnormalities at imaging. In two cases, 3-ortho-methyldopamine was increased (first one at 1.4 N and the second at 6.7 N but in a context of vaso-vagal episode with normal result at further control). In the ten others, NMA was moderately increased at 1.4±0.2 N as a mean. Medications were identified as a confounding factor in four patients (β-adrenergic receptor blockers and tricyclic antidepressant). The others had normal results at subsequent determination.

Abnormal imaging

Sixteen (9.7%) abnormal imaging were incidentally diagnosed: four gastrointestinal stromal tumor (GISTs); two unilateral adrenal hyperplasia; one bilateral adrenal hyperplasia; three extra-adrenal nodules with one renal oncocytoma and two neurofibromas; and six adrenal nodules including one myolipoma, three adenomas (spontaneous density <10 UH, washout >60%) and two unspecified nodules.

Patient characteristics with GIST were as follows: three men and one woman, age at diagnosis 50±12 years, asymptomatic, localized to the small intestine, and tumor size 55.5±3.3 mm. Three patients underwent surgery, the last patient had only biopsy because he was contraindicated for surgery, and two of them had adjuvant treatment by imatinib. All tumors were negative for KIT and PDGFR.

Scintigraphy

In total, 23 scintigraphies were performed in 22 patients: three patients underwent 123I-MIBG scintigraphies, 18 patients [18F]-FDOPA PET-CT and one patient both examinations.

The four patients submitted to 123I-MIBG presented with elevated urinary metanephrines. 123I-MIBG scintigraphy was positive in two patients with a secreting PHEO, visualized by CT and histologically proven after tumor resection (patients 3 and 6). In patient 6, catecholamine secretion was symptomatic with a treated hypertension. In patient 3, 123I-MIBG was considered positive in a 25 mm adrenal lesion observed on CT.

From the 19 [18F]-FDOPA PET-CT, ten were positive leading to the diagnosis of PHEO, including four secreting PHEOs (patients 1, 2, 4 and 5) and the six non-secreting PHEOs. All patients with a positive scintigraphy had an adrenal lesion on abdominal CT. The nine remaining examinations were negative.
Six were realized because of adrenal lesion at abdominal CT and three because of elevated urinary metanephrines. From the four secreting PHEOs, one symptomatic patient (patient 1) demonstrated an intense 18F-DOPA uptake in a 16 mm nodule on the left adrenal gland and a lower tracer uptake in an 8 mm thick right adrenal gland nodule suggesting a bilateral PHEO (Fig. 3). Concerning non-secreting PHEO, three patients demonstrated intense 18F-DOPA uptake in adrenal lesions sizing 11, 16 and 26 mm (patients 10, 11 and 9 respectively). The lesion of 26 mm in patient 9 has been removed and corresponds with a PHEO.

In none of the patients, the scintigraphy examination found abnormal tracer uptake outside the adrenal glands that could be consistent with ectopic PHEO.

### Table 3 Characteristics of patients with secreting and non-secreting pheochromocytoma.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at diagnosis (years)</th>
<th>Symptoms</th>
<th>Urinary fractionated metanephrines</th>
<th>Tumor size on CT (mm)</th>
<th>Scintigraphy</th>
<th>NF1 manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MA (N)</td>
<td>NMA (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secreting pheochromocytoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>54</td>
<td>HTN, headache</td>
<td>1.0</td>
<td>3.6</td>
<td>16</td>
<td>18F-FDOPA TCL, SFF, C-NF, learning difficulties</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>53</td>
<td>None</td>
<td>1.4</td>
<td>2.4</td>
<td>19</td>
<td>18F-FDOPA TCL, C-NF, pseudarthrosis, P-NF, learning difficulties</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>77</td>
<td>None</td>
<td>2.0</td>
<td>2.1</td>
<td>25</td>
<td>123I-MIBG TCL, C-NF, scoliosis, vertebral dysplasia, basocellular carcinoma</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>34</td>
<td>None</td>
<td>4.9</td>
<td>1.2</td>
<td>30</td>
<td>18F-FDOPA TCL, SSF, C-NF and SC-NF with nerve compression, optic pathway glioma</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>57</td>
<td>None</td>
<td>2.0</td>
<td>3.4</td>
<td>28</td>
<td>18F-FDOPA TCL, SFF, C-NF, P-NF, Lisch nodules, UBOs</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>57</td>
<td>HTN</td>
<td>7.6</td>
<td>3.9</td>
<td>33</td>
<td>123I-MIBG TCL, SFF, C-NF</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>–</td>
<td>–</td>
<td>3.2 ± 2.6</td>
<td>2.8 ± 1</td>
<td>25.2 ± 6.6</td>
<td>–</td>
</tr>
</tbody>
</table>

Non-secreting pheochromocytoma

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at diagnosis (years)</th>
<th>Symptoms</th>
<th>Urinary fractionated metanephrines</th>
<th>Tumor size on CT (mm)</th>
<th>Scintigraphy</th>
<th>NF1 manifestations</th>
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</tr>
<tr>
<td>7</td>
<td>F</td>
<td>51</td>
<td>None</td>
<td>0.4</td>
<td>0.8</td>
<td>6</td>
<td>18F-FDOPA Lisch nodules, P-NF, PHEO, jejunal GIST</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>60</td>
<td>None</td>
<td>1.0</td>
<td>0.8</td>
<td>15</td>
<td>18F-FDOPA TCL, SFF, C-NF, polynuropathy</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>61</td>
<td>None</td>
<td>1.0</td>
<td>0.9</td>
<td>26</td>
<td>18F-FDOPA SFF, C-NF, P-NF, MPNST</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>35</td>
<td>None</td>
<td>0.9</td>
<td>0.6</td>
<td>11</td>
<td>18F-FDOPA TCL, SFF, C-NF, P-NF</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>76</td>
<td>None</td>
<td>0.9</td>
<td>0.7</td>
<td>16</td>
<td>18F-FDOPA TCL, SFF, C-NF and SC-NF</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>36</td>
<td>None</td>
<td>0.8</td>
<td>0.7</td>
<td>10</td>
<td>18F-FDOPA TCL, SFF, C-NF and SC-NF, P-NF with congenital glaucoma</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>–</td>
<td>–</td>
<td>0.85 ± 0.2**</td>
<td>0.75 ± 0.1***</td>
<td>14 ± 6.9****</td>
<td>–</td>
</tr>
</tbody>
</table>

C-NF, cutaneous neurofibroma; CT, computed tomography; HTN, high blood pressure; MA, metanephrine (N = 1500 nmol/24 h); MPNST, malignant peripheral nerve sheath tumor; NMA, normetanephrine (N = 2200 nmol/24 h); P-NF, plexiform neurofibroma; SC-NF, sub-cutaneous neurofibroma; SFF, skin-fold freckling; TCL, café au lait patches; UBOs, unidentified bright objects at MRI.

*P = 0.805, **P = 0.055, ***P = 0.0008 and ****P = 0.0165 for the comparison by unpaired Student’s t-test with secreting pheochromocytoma. Patient 6 and patient 8 had beta blocker treatment.

### Surgery

Three patients with secreting PHEO underwent surgery after medical preparation (patients 2, 3 and 6) and one patient with non-secreting PHEO because of tumor size >2 cm (patient 9). There were no per- or post-operative complications, and all urinary fractionated metanephrines were normalized after surgery in secreting PHEO. The post-operative follow-up duration was 15, 6, 24 and 3 months respectively. Surgery is also planned for patient 1 and is under consideration for patients 4 and 5. Three PHEOs presented one criteria of aggressivity at pathological examination with capsular invasion, and the last one presented two criteria with one atypical mitotic figure and adipose tissue invasion. Ki-67 was <1% in all
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Discussion

In this study, the prevalence of PHEO in NF1 patients was found to be 7.7%, which is well above that reported in previous studies (5, 6). This may be, at least partly, explained by the lack of symptoms (84% of asymptomatic PHEO) and the non-secreting nature of a large part of detected PHEO (50%), already described in 2013 by Haissaguerre et al. (11) in a retrospective study performed in sporadic PHEO. In the literature, the age at onset of PHEO is typically the fourth decade of life, both in NF1-associated and sporadic cases (12, 13), without influence of gender. In our study, age at diagnosis is a little bit higher, at 55.3 ± 13.7 years, for secreting PHEO and 53.2 ± 15.9 years for non-secreting PHEO, without significant difference. However, as a large part of PHEO is asymptomatic and/or non-secreting, diagnosis is probably delayed.

In a study in 2006, conducted on a large European registry of patients with PHEO, including 25 NF1 patients, Bausch et al. (14) found bilateral PHEO in 20% of NF1 patients, all were adrenal originated without ectopic PHEO and 12% were malignant (presence of metastases). The characteristics of patients with PHEO related to NF1 were similar to those of patients with sporadic PHEO except for multifocal localization and malignancy. Our results are somewhat different with two cases of bilateral PHEO (16.6% of diagnosed PHEO) and no malignancy, but all diagnosed PHEO were adrenal too. However, the study population was not the same, and our follow-up duration was probably too short to diagnose metastases.

It has been reported that the amounts of catecholamines released by secreting PHEO resulting in hypertension were positively correlated with their size (15, 16). In this study, tumor size of secreting PHEO was significantly higher than that of non-secreting PHEO, but there was no correlation between metanephrine secretion and tumor size of secreting PHEO. However, only two out of the six patients with a secreting PHEO presented with hypertension. All of them secreted MA and/or NMA, as it is classically reported in NF1 patients (17).

Concerning biochemical testing for diagnosis of PHEO, the Endocrine Society recommends that initial biochemical testing should include measurements of plasma-free metanephrines or urinary fractionated metanephrines (7). Indeed, as shown by Perry et al. (18), measurement of urinary fractionated metanephrines by mass spectrometry provides excellent sensitivity (97%) and specificity (91%) for diagnosis of PHEO. Plasma-free metanephrine measurement has been reported to have better performances than urinary fractionated...
metanephrines, especially better sensitivity (19). However, it is more expansive, not reimbursed in all countries and less available, which could be problematic in a systematic screening approach. We have chosen a threshold of 2 N for secreting PHEO to eliminate the false positives and improve the sensitivity of screening since we were in a systematic screening approach. All patients with MA and/or NMA >2N were diagnosed with a secreting PHEO and all false positives were <1.5 N, essentially with elevated isolated NMA. In most cases, this was explained by essential hypertension and medications as beta blockers and tricyclic antidepressants (20, 21).

Anatomical imaging performed in this study was abdominal ultrasound in non-overweight patients (BMI <25 kg/m²) or in case of CT refusal, and abdominal CT in the others or in case of abnormal abdominal ultrasound. CT is recommended as the first-choice imaging modality for the localization of PHEO and paraganglioma (7) because of its excellent spatial resolution for thorax, abdomen and pelvis with sensitivity between 88 and 100% (22, 23, 24). Moreover, 20% of PHEO and paraganglioma is revealed by acute emergency situation with end-organ damage. In these cases, biochemical diagnosis of PHEO suffers drawbacks because of delays in provision of results and false positive in such form of stress; that is why abdominal CT is more appropriate to locate a tumor and to adapt therapeutic management (25).

However, in a systematic screening approach, ultrasound could be considered as a less invasive examination, with correct performances. According to Krawjeska et al. (26), its specificity considering adrenal gland evaluation is estimated at 92%, whereas its sensitivity is estimated at 76%, lower in case of left-sided tumors, those <2 cm in diameter, and in obese patients. In this study, two out of the 27 ultrasounds were positive – one case of secreting PHEO (patient 2) and one case of non-secreting PHEO (patient 7).

Concerning functional imaging, patients with elevated urinary fractionated metanephrines and/or a lesion at abdominal CT underwent a scintigraphy. Sensitivity of 123I-MIBG scintigraphy ranges between 85 and 88% for PHEO, whereas specificity ranges from 70 to 100% (27, 28). In a meta-analysis of 15 studies of 123I-MIBG scintigraphy, sensitivity was 94% and specificity was 92% (29). Newer compounds such as [18F]-FDOPA PET-CT have been described to outperform 123I-MIBG scintigraphy in the detection of PHEO, with a sensitivity of 100% for [18F]-FDOPA PET-CT and 71% for 123I-MIBG scintigraphy (22, 30, 31), particularly in paraganglioma and metastatic disease. Moreover, [18F]-FDOPA PET-CT has other advantages – no necessity of thyroid blockage and interruption of antihypertension medication, and only 1-day procedure. This could be a bias in our study, as smaller lesions could be better diagnosed with [18F]-FDOPA PET-CT than with 123I-MIBG scintigraphy. However, only four 123I-MIBG scintigraphies were performed (including one patient with both examinations) vs 19 [18F]-FDOPA PET-CT, and two of them have been conducted to diagnose PHEO.

Concerning peri-operative medical management, the US Endocrinology Society suggests α-adrenergic receptor blockers as the first choice. However, some studies have suggested that the use of calcium blockers was safe and associated with a low morbidity and mortality (32, 33, 34).

The main limitations of our work is the lack of urinary creatinine measurement to verify the completeness of the urine collection for urinary fractionated metanephrine evaluation, and the lack of standardization of abdominal CT protocol, as examinations were realized in different radiology centers. Nevertheless, radiologists were informed to explore adrenal glands. As expected, our approach had led us to the diagnosis of several adrenal incidentalomas. Their prevalence was rather high – 9.7% – compared with that usually reported in the general population from radiological series (between 0.3 and 4.4%) (32, 33), raising the question of follow-up to apply. We also incidentally diagnosed a GIST in four patients without PHEO, corresponding to 1.7% of patients. This is not surprising as GISTs are known to occur in patients with NF1 with a prevalence estimated between 4 and 25% (34, 35). All patients were asymptomatic, as it is classically observed with only 5% of symptomatic cases (36); no expression of KIT and PDGFRA was found (37).

Nevertheless, in this study, systematic screening led to the diagnosis of 12 PHEO. Only two of them would have been diagnosed using the conventional strategy to explore only symptomatic patients. It is crucial to identify these tumors for several reasons (7). First, PHEOs are classically recurrent in genetic syndrome, including NF1, with a proportion between 10 and 20% (9, 12, 14). Therefore, adrenocortical sparing surgery represents a major concern and has gained popularity in the last few years in various indications (38, 39, 40). First, this technique could be applied only in case of small lesion (usually smaller than 2 cm), hence the importance of early diagnosis. Secondly, even if it is rare, PHEO may have a malignant potential, defined as the presence of metastases in nonchromaffin tissue (41). Discordant results have been reported on the prevalence...
of malignant PHEO in NF1. In large series, the metastatic potential of PHEO was estimated to be around 10% (12, 14). By contrast, Zinnamosca et al. in 2011 (9) found no malignant PHEO in a small series of 48 patients. Finally, as observed in this study, secreting PHEO can be asymptomatic. Lafont et al. (42) demonstrated in a cohort of 50 patients that normotensive PHEO have roughly comparable per-operative hemodynamic instability to hypertensive PHEO and differ markedly from non-PHEO adrenal incidentalomas. It is therefore crucial to identify normotensive PHEO when surgery is scheduled and to apply the standard of care for PHEO anesthesia. Surprisingly, we found in this series that 50% of PHEO was not secreting. A patient with a large PHEO more than 2 cm underwent surgery, but the others were followed on. The natural history of these PHEO is not well known and whether these non-secreting tumors will become secreting, rapidly progressive, or at risk of malignancy remains to be determined to clearly assess the cost–benefit ratio of such a strategy and the modalities of the follow-up. For now, we would suggest performing screening every 4–5 years after 40 years of age.

This is the biggest prospective study of prevalence of PHEO in patients with NF1. Our results suggest a clear underestimation with a prevalence classically evaluated at 1% vs 7.7% in our study, explaining all the consensus recommending screening only symptomatic patients (7, 8, 43). The large part of non-secreting PHEO, usually scarce, raises the question of the treatment and the follow-up to achieve. Some elements suggest an interest of diagnosis of these non-secreting PHEO, as we discussed earlier, with medical preparation in case of other surgery to prevent per-operative complications, and to initiate a follow-up of these lesions. However, the benefit of this strategy is not clearly demonstrated, especially concerning the cost/benefit aspect.

In conclusion, PHEO in NF1, whether or not secreting, are often asymptomatic. The current strategy to explore only symptomatic patients leads to an underestimation of prevalence with the risks inherent to the existence of unrecognized PHEO. Therefore, PHEO screening may be proposed to all NF1 patients older than 40 years, with metanephrine quantitative analysis and imaging based on CT or MRI to lower patient irradiation. Further studies are needed to assess this proposition, the evolution of these lesions, in particular non-secreting lesions, and their therapeutic management.

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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Pheochromocytoma in neurofibromatosis type 1

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Clinical Study

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Pheochromocytoma in neurofibromatosis type 1


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