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Screening for Early Asymptomatic Pheochromocytoma in MEN-2

Margareta Telenius-Berg,* Bertel Berg, Bertil Hamberger, and Sten Tibblin

Pheochromocytomas in multiple endocrine neoplasia type 2 (MEN-2) have a serious prognosis with high mortality if not treated early. Ten percent of MEN-2 patients who sought medical advice for symptoms of medullary thyroid carcinoma (MTC) and/or pheochromocytoma died from the latter tumor, and another 24% died from MTC, according to retrospective analysis (1). One of three patients with symptomatic pheochromocytoma died from this tumor. The mean age at death in our 46 Swedish MEN-2 patients with pheochromocytoma was 41 years (1). Mortality from MTC has been markedly reduced by screening, early diagnosis, and treatment. An important future goal of family screening is early diagnosis and treatment of the adrenal tumors in MEN-2.

Problems in Diagnosing Pheochromocytoma
Clinical symptoms are varied and most unreliable as indicators of the diagnosis. The majority of our patients did not have the classical paroxysmal symptoms combined with hypertensive crises. Many of our patients even denied symptoms before surgery: they had become used to fatigue, spells of tachycardia, and sweating. Clinical diagnosis has a low sensitivity and many false-negative and false-positive diagnoses are common. The most important differential diagnosis—by far outnumbering pheochromocytoma—is neurovegetative lability or "hyperdynamic beta-adrenergic state" (2). These patients have clinically and biochemically a "phenotypic pheochromocytoma syndrome."

Is screening for asymptomatic pheochromocytoma indicated?
This concern seems to parallel discussions of MTC in the 1970s: What is the proper approach to patients with high serum calcitonin but no identifiable tumor—"wait-and-see" or surgery? After a prospective follow-up we were able to show that both morbidity and mortality decreased after active screening for MTC (1). Pheochromocytoma is a potentially life-threatening tumor in which the first symptoms may be missed and cardiovascular hypertensive crises may come without warning. In our opinion screening for early pheochromocytoma presents several advantages:
1) Early diagnosis and operation will decrease the risk of cardiovascular crises in association with childbirth, surgery, or unexpected accidents.
2) Early detection of adrenal disease allows the possibility to choose subtotal adrenalectomy with preservation of the adrenal cortex (3). Furthermore, we have advocated the use of unilateral adrenalectomy in cases where tumor development is highly asynchronous and where one adrenal seems free from tumor (4).
3) Diagnostic screening is also important as a means of increasing our knowledge of the natural history of this component of the MEN-2 syndrome.

With few exceptions (5) most previous diagnostic experience has been gained from studies of sporadic pheochromocytomas and those conclusions may not be transferable to the pheochromocytomas in MEN-2.

Diagnostic techniques
Even in symptomatic pheochromocytoma the diagnosis cannot be made purely on clinical grounds. Biochemical and morphological techniques for localization of the tumor(s) are needed but no single method combines both high sensitivity and high specificity. Combinations of diagnostic methods are required but little experience or data are available for the asymptomatic patient with adrenal medullary hyperplasia or early tumors.

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Biochemical techniques
Tests for the hormones produced by the adrenal tumor(s) are the starting point. For MTC diagnosis, the calcitonin (CT) peptide has the advantage of being fairly stable. In contrast, plasma catecholamine specimens need rapid and meticulous handling by experienced staff. Plasma levels fall within minutes after an in vivo surge. In vitro their instability is the most severely limiting factor for obtaining reliable results. Many different methods for catecholamine assay are available, but only a few have been properly validated and large discrepancies may occur between laboratories (6).

Another problem is the normal fluctuation of plasma levels after even minor stress, which can cause false-positive results. Even in pheochromocytoma, catecholamine release is intermittent, and basal plasma levels are not consistently raised (7,8).

Consequently, urine analysis of catecholamines and their metabolites remains the cornerstone of screening programs in most centers. Diagnostic efficiency has been improved by the introduction of new analytical methods. Gagel et al (5) have emphasized that an increased epinephrine/norepinephrine ratio in urine is typical for early hereditary pheochromocytoma. Unfortunately, poor patient compliance in collecting 24-hour urine samples is common and interaction with antihypertensive drugs is an increasingly common problem.

Provocative (stimulation/inhibition) tests
Older pharmacological testing with histamine and phen tolamine has almost been abandoned because of low diagnostic accuracy and the risks of serious complications. In our experience, even the glucagon stimulation test does not have the desired sensitivity and specificity. The clonidine suppression test introduced by Bravo et al (9) seems to be able to discriminate pheochromocytoma from other causes of catecholamine excess. This centrally acting alpha-adrenergic antagonist suppresses neurogenically-mediated release of catecholamines but not the autonomous secretion from adrenal medullary tumors. Sensitivity and specificity are high in sporadic symptomatic tumors with high norepinephrine secretion. Since the pheochromocytomas in MEN-2 appear to have a different secretory pattern (predominantly epinephrine), only empirical trials can evaluate the sensitivity of this procedure in MEN-2.

Exercise test
No pharmacological test for diagnosing pheochromocytoma has gained general acceptance. Since any manipulation of patients with adrenal tumors (whether it be pharmacological or with a more physiological test such as exercise) involves risk taking, the aim should be to find as safe a test as is consistent with good diagnostic efficiency.

Physical exercise may provoke release of plasma catecholamines both in healthy subjects and in pheochromocytoma patients. This was the basis of the exercise test which we recently proposed (10). This procedure might also provide information on the risks of physical exercise in everyday life for patients without clinical symptoms.

Our aim was to find a practical, simple, noninvasive provocative test which would satisfy the requirements listed in Table 1 and would also be suitable for individuals of varying ages and degrees of physical fitness.

In healthy subjects elevation of plasma epinephrine occurs predominantly when the patient approaches exhaustion and then at the onset of anaerobic metabolism (11). To minimize risks we should stop short of that stage. In standardizing the work load the patients were allowed to work until "really tired" but not yet "exhausted," ie, to a level of submaximal exercise.

Patients and Methods
Twenty-six MEN-2 gene carriers were examined. Eight of these had asymptomatic pheochromocytoma(s) (the smallest tumor verified by operation was 9 mm in diameter). Nine had undergone surgery for MTC but had no clinical or biochemical evidence of pheochromocytoma. Four patients had had unilateral adrenalectomy and six patients had had bilateral adrenalectomy without evidence of new or residual pheochromocytoma.

Seventeen clinically healthy individuals (age- and sex-matched to the 17 patients in the pheochromocytoma and MTC groups) served as controls, as did 11 patients with neurovegetative lability who had symptoms mimicking pheochromocytoma. In this latter group, pheochromocytoma had been ruled out by current diagnostic tests (in some patients including computed tomography) over at least a two-year follow-up.

The stress test was performed on an electrically-braked bicycle ergometer. The work load was increased continuously until the patient felt uncomfortable fatigue but not extreme exhaustion. Heart rate, blood pressure, and ECG were recorded.

Blood samples for basal (pre-exercise) plasma catecholamine analysis were drawn from an indwelling venous catheter after the patient had rested for 30 minutes in a supine position. Postexercise catecholamine samples were drawn immediately after exercise with the patient lying down beside the bicycle. The patients were nonfasting to avoid a hypoglycemic rise in catecholamines. Plasma catecholamines were analyzed by high performance liquid chromatography using electrochemical detection (12).

Results
The wide variation in the increments of all three plasma catecholamines after exercise probably reflects the degree of exhaustion during the test. For norepinephrine and dopamine both
basal and postexercise levels were about the same for all three groups (Fig 1). Subjects with neurovegetative lability tended to have higher dopamine levels after work.

Healthy controls and bilaterally adrenalectomized patients did not differ significantly in norepinephrine and dopamine increments, blood pressure, or heart rate during work. We conclude that at least the main contribution of norepinephrine and dopamine is extra-adrenal sources. Norepinephrine and dopamine levels after exercise probably reflect sympathetic nerve activity.

Epinephrine differed from the other plasma catecholamines. Basal levels were higher than for the controls in two groups: five out of eight pheochromocytoma patients and four out of 11 neurovegetative lability patients. The highest level for the healthy controls (0.15 nmol/L) was chosen as the cutoff point. Thus, a clear overlap was seen between the two groups of clinical importance, pheochromocytoma and pheochromocytoma-like neurovegetative lability (Fig 1).

Postexercise plasma epinephrine levels increased markedly in all groups except in the bilaterally adrenalectomized patients in whom there were no increments at all. This indicates that practically all epinephrine, especially that released during exercise, originates in the adrenal glands (Fig 1).

During work the pheochromocytoma patients increased their epinephrine levels most, significantly higher than for both healthy controls and neurovegetative lability patients (p < 0.001). Six out of eight pheochromocytoma patients had levels higher than the cutoff point (2 nmol/L), as had one of nine MTC patients, two of 17 healthy controls, but none of the 11 neurovegetative lability patients.

**Postexercise epinephrine/dopamine ratio**

After work epinephrine/dopamine ratios also were significantly higher in the pheochromocytoma patients than in healthy controls (p < 0.001) or patients with neurovegetative lability (p < 0.001). With an arbitrary cutoff point at six, a high ratio was seen in seven out of seven assessable patients with pheochromocytoma (an eighth patient could not be evaluated because of L-DOPA treatment). High ratios were also seen in three of 17 healthy controls and five out of nine MTC patients, but not in any of the patients with neurovegetative lability nor those who had had unilateral or bilateral adrenalectomy (Table 2).

The results can also be plotted as in Fig 2. The clear separation between the pheochromocytoma and neurovegetative lability groups was even greater if the relatively high dopamine level for the latter group was taken into account (Fig 2).
Table 2

Plasma Catecholamine Levels Before and After Exercise

<table>
<thead>
<tr>
<th></th>
<th>Pheochromocytoma</th>
<th>Neurovegetative Lability</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epinephrine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before: mean</td>
<td>0.3</td>
<td>0.14</td>
<td>0.07</td>
</tr>
<tr>
<td>median</td>
<td>0.24</td>
<td>0.09</td>
<td>0.06</td>
</tr>
<tr>
<td>range</td>
<td>0.05 to 0.8</td>
<td>0.05 to 0.34</td>
<td>0.03 to 0.12</td>
</tr>
<tr>
<td>After: mean</td>
<td>3.6</td>
<td>0.49</td>
<td>1.22</td>
</tr>
<tr>
<td>median</td>
<td>2.8</td>
<td>0.28</td>
<td>0.86</td>
</tr>
<tr>
<td>range</td>
<td>1.3 to 9.5</td>
<td>0.07 to 1.53</td>
<td>0.05 to 6.4</td>
</tr>
<tr>
<td><strong>Epinephrine/dopamine ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before: mean</td>
<td>2.7</td>
<td>1.50</td>
<td>1.39</td>
</tr>
<tr>
<td>median</td>
<td>3.9</td>
<td>1.14</td>
<td>1.25</td>
</tr>
<tr>
<td>range</td>
<td>0.20 to 4.5</td>
<td>0.23 to 4.5</td>
<td>0.08 to 5.0</td>
</tr>
<tr>
<td>After: mean</td>
<td>21.7</td>
<td>1.45</td>
<td>4.06</td>
</tr>
<tr>
<td>median</td>
<td>14.8</td>
<td>1.13</td>
<td>3.1</td>
</tr>
<tr>
<td>range</td>
<td>6.7 to 50</td>
<td>0.24 to 3.7</td>
<td>0.26 to 12</td>
</tr>
</tbody>
</table>

Although our pheochromocytoma patients were asymptomatic, five out of eight had raised basal plasma epinephrine levels, ie, sensitivity was 0.6. Specificity was suboptimal (0.6) in respect to the group with neurovegetative lability: several false-positive results were seen. This illustrates that it is not sufficient to have a good discrimination versus healthy controls but that one should include a control group of patients presenting clinical difficulties in diagnostic work.

The postexercise epinephrine/dopamine ratio completely separated patients with pheochromocytoma from those with neurovegetative lability. The syndrome of neurovegetative lability seems to be associated with increased basal levels of plasma catecholamines but the response to exercise is subnormal.

The cardiovascular response did not differ between pheochromocytoma patients and the other groups. It therefore seems probable that moderate exercise in asymptomatic patients with MEN-2 pheochromocytoma does not carry a great risk for severe cardiovascular reactions.

**Imaging techniques**

Clinical chemistry techniques are primarily used to diagnose the presence of a catecholamine-producing tumor. The next step is to verify the diagnosis and localize the tumor. Imaging techniques should rarely be used as first line examinations of the patient with suspected pheochromocytoma. Despite their advantages, these methods were not intended nor are they suitable for repeated regular screening of MEN-2 families. Arterial angiography has been replaced by newer techniques. Venous catheterization for sampling plasma catecholamines is seldom needed in MEN-2 pheochromocytoma, as this is primarily a tumor of the adrenal medulla. Computed tomography has been a great diagnostic advance. Sensitivity is high if the tumor is larger than 10 mm in diameter. However, even with much experience, interpretation is often difficult in small tumors.

Meta-iodo-benzylguanidine (MIBG) scintigraphy and computed tomography are complementary (13). MIBG is taken up in neuroectodermal tissues and thus provides both morphological and metabolic evidence of a chromaffin tumor. In our experience with pheochromocytomas in MEN-2, MIBG provides good results with tumors 15 mm or more in diameter. The practical problems in MIBG use involve availability, cost, and the need to stay several days in the hospital. The radiation dose is high both for computed tomography and for MIBG and therefore they cannot be used for repeated screening in young, fertile individuals.

**Acceptability of screening for pheochromocytomas**

Most members of MEN-2 families are aware of the morbidity and mortality of the syndrome and of the rationale for screening measures aimed at early diagnosis and therapy. Compliance with screening is therefore very good. To achieve full acceptability the screening test must meet the criteria listed in Table 1. MEN-2 families are a high-risk population. This is a major factor in raising the predictive value of a positive test. With rare exceptions, the MTC tumor will be the first tumor to develop and it can be detected and diagnosed early in life. Therefore, MTC may be considered a specific marker for probable future development of the adrenal tumors, and screening for pheochromocytoma may be restricted to the documented carriers of the MEN-2 gene.
Conclusion

We believe that screening for asymptomatic pheochromocytoma in MEN-2 is indicated, just as for MTC. This will have advantages both for the individual patient as well as for our understanding and management of the syndrome as a whole. The new stress test using physical exercise seems to have better diagnostic efficiency than measurement of basal plasma catecholamine levels only. The epinephrine/dopamine ratio seems valuable, especially for the clinically important differential diagnosis of neurovegetative lability.

Acknowledgments

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