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Screening for Pheochromocytoma in the MEN 2 Syndrome

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Twenty-two patients with the multiple endocrine neoplasia type 2 (MEN 2) syndrome were screened for pheochromocytoma since it is a major cause of morbidity in MEN 2 families. Clinical symptoms, biochemical parameters, ultrasound, computed tomography or magnetic resonance imaging, and meta-iodo-benzylguanidine (MIBG) scintigraphy were evaluated for detection of adrenal tumors. Clinical symptoms and plasma or urine catecholamines appeared to be nonspecific, whereas MIBG scintigraphy was highly specific and the most sensitive parameter. Patients older than age 30 should be scintigraphically screened at least once despite the radiation exposure. Demonstration of only slight uptake is not an indication for surgery but rather for careful follow-up. (Henry Ford Hosp Med J 1989;37:129-31)

While it is undisputed that families must be screened when a multiple endocrine neoplasia type 2 (MEN 2) syndrome is found in any member, the importance of a systematic search for pheochromocytomas in these families has been underestimated. In a large MEN 2 family in West Germany (L-kindred), many members have died of pheochromocytoma. Initially the cause of sudden death in the family members could not be explained, but retrospectively the symptoms suggested an undetected pheochromocytoma. The occurrence of a pheochromocytoma may not be common, but adrenal involvement as well as thyroid cancer in MEN 2 families can be fatal. The possibility of pheochromocytoma is present especially when there is a history of pheochromocytomas in older MEN 2 family members. (A pheochromocytoma can also be found in children sooner than in parents.)

The age of onset for medullary thyroid cancer (MTC) and pheochromocytoma in our patients (Figure) suggests that pheochromocytomas can be detected by age 30. Cases in which a pheochromocytoma was detected at a much later age probably reflect incomplete workup or follow-up. However, the age of clinical detection may vary in the different families. In an effort to determine the best method for detecting adrenal tumors, we evaluated 22 patients with MEN 2.

Methods

Clinical symptoms of pheochromocytoma include headache, excessive perspiration, palpitations, weakness, blurred vision, spells of dizziness, and hypertension (1,2). Patients who had had surgery for pheochromocytoma were questioned about their preoperative symptoms. Serum catecholamine levels were measured. For combined norepinephrine and epinephrine levels, values below 500 ng/L are considered negative and values above 2,000 ng/L are considered positive for detection of a pheochromocytoma. Ultrasonography was done with a 3.5 MHz real-time scanner (Picker LS 3200). Computed tomography was performed with different units (mostly SOMATOM DR), with a slice thickness of 4 mm and without contrast media. In magnetic resonance imaging (MRI) (MAGNETOM, 1.0 Tesla field strength), T1- and T2-weighted sequences were used, partly with Gado-linium-DTPA for contrast examinations. Before 1987, meta-iodo-benzylguanidine (MIBG) scintigraphy was done with 20 MBq 123I MIBG with scans after 48 or 72 hours; later, with 250 MBq 123I MIBG (Amersham Buchler, Braunschweig, West Germany), a total body scan and an emission computed tomography study were performed 24 hours after injection. Details and radiation exposure are listed in the Table (3).

Results

Of 12 patients operated on for a pheochromocytoma, three had a typical clinical presentation and the others were asymptomatic or lacked sufficient symptoms to cause suspicion. Clinical symptoms included headache (three patients), excessive perspiration (five patients), palpitations (six patients), nervousness (five patients), nausea (one patient), blurred vision (one patient), spells of dizziness (one patient), and hypertension (seven patients).

In typical cases the measurement of serum or urine catecholamines is diagnostic. In four of ten patients, the serum values were higher at times than 2,000 ng/L (range: 1,006 to 6,340...
ng/L; median: 1,795 ng/L), and the sizes of the pheochromocytomas ranged between 20 and 70 g. Overlap with normal values is seen in MEN 2 patients with negative MIBG scans (n = 11; range: 627 to 1,180 ng/L; median: 997 ng/L) and in sporadic MTC with negative MIBG scans (n = 11; range: 600 to 1,550 ng/L; median: 909 ng/L).

Sonography and scintigraphy could be compared in 20 cases. Positive and negative results corresponded in nine patients and seven patients, respectively. Three patients with positive scintigrams were sonographically negative; in one patient a sonographically detected lesion did not accumulate MIBG.

Computed tomography and MRI could be compared with scintigraphy in 18 patients. In ten patients a lesion could be detected with both MIBG and computed tomography or MRI, in three patients it could be excluded. In two cases computed tomography or MRI showed slight changes which did not accumulate MIBG, and in three cases an increased MIBG uptake could not be ascribed to a detectable lesion.

**Discussion**

In our patients the typical symptoms (1,2) did not occur frequently: nervousness in young women or hypertension in older men generally do not suggest a pheochromocytoma.

In a 62-year-old patient who had an abnormal pentagastrin calcitonin test (0.3 to over 4.6 µg/L calcitonin) in the family screening, all imaging methods showed a huge adrenal tumor which weighed 70 g when removed before resection of the thyroid gland. The only symptom was mild hypertension (170/100 mm Hg). He had been hospitalized for six months because of carcinoma of the stomach and prostate and for hip replacement. The pheochromocytoma, not detected during that hospitalization, was discovered later on direct search. This case again confirms that clinical symptoms are not specific for pheochromocytoma.

Very high catecholamine levels are unequivocal for a pheochromocytoma, but pheochromocytomas could be found in only some of our patients with such high levels; a significant overlap with normal patients exists. There are also other causes for increased catecholamine levels: among the patients with sporadic MTC, a patient with a MIBG-accumulating thyroid tumor had one of the highest catecholamine levels. In one symptomatic patient with an adrenal tumor of 5 x 2 cm, proved by different imaging methods, the clonidine stimulation test was negative, and thus an operation had not been advised (4). In this case the clonidine test did not contribute to early detection of pheochromocytoma.

In paroxysmal secretion of catecholamines, serum determinations can be normal in the interval, and in 24-hour urine collections very slight increases may not be detected. To improve detectability, stimulation of the catecholamine reserve by exercise was suggested (5,6), but this method is time-consuming and not always unequivocal.

The goal of the screening procedure is to find pheochromocytomas of small size, not when they have reached a volume of 70 mL as in the 62-year-old patient discussed. Of the different imaging modalities, MIBG scintigraphy is capable of detecting very small tumors. This is achieved best either by using a greater amount of 123I MIBG or by imaging much later after application of the 123I-labeled substance (7,8). However, it is sometimes difficult to separate normal individuals from those with symmetrical hyperplastic adrenals, because a minimal accumulation of 123I MIBG can be seen after 24 to 48 hours in normal individuals (9). The differentiation becomes easier when a left/right difference is seen. Quantitative uptake determination can be helpful (10). Generally, the degree of uptake does not correlate well with the amount of serum catecholamines because the uptake of the tracer and the synthesis and secretion of catecholamines are related to different cell functions (11). A marked uptake in the adrenal medulla with normal catecholamine levels has been seen, and increased levels without MIBG uptake can be due to scattered single cells in metastasizing pheochromocytoma. A comparison of scintigraphy and sonography, or scintigraphy, computed tomography, and MRI yields almost the same results in detecting lesions (12). Due to anatomical reasons, sonography is not as good as scintigraphy in detecting small left-sided lesions, especially in obese patients. In children the normal adrenal usually can be differentiated from the abnormal adrenal by secondary morphological features (13).

The advantage of MRI is in the high soft-tissue contrast which allows identification of tissues without the use of contrast medium (14,15). Moreover, the different slice reconstructions make
the orientation easier. The advantages of computed tomography are its short acquisition time and good spatial resolution. A preferred method for examination of the adrenals has not yet been established (12). Discrepant findings to scintigraphy occur in very small lesions (< 1.5 cm) (16). Due to the high sensitivity of MIBG scintigraphy, even hyperplasia of the adrenal medulla can be detected (17). However, surgical exploration is not indicated in asymptomatic patients with normal catecholamine levels until positive findings can be confirmed. In this way patients at risk can be found early and a careful follow-up is possible.

Conclusions

Screening for pheochromocytoma is necessary in MEN 2 patients even when no clinical symptoms exist because pheochromocytoma may be fatal if untreated. Laboratory tests and sonography alone are not reliable in confirming or excluding pheochromocytomas. MIBG scintigraphy as a functional method is very sensitive and specific in detection of hormone active lesions of the adrenal medulla. Despite the radiation exposure, scintigraphy should be performed at least once, preferably with 250 MBq 123I MIBG in single photon emission computed tomography. A slight uptake in the adrenals is not an indication for surgery but does suggest a more careful follow-up surveillance of catecholamine levels and clinical symptoms.

References