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Pheochromocytoma is a frequent indicator of multiple endocrine neoplasia type 2A (MEN 2A); in the 35 French MEN 2A families in which a pheochromocytoma occurred first in some affected members, 30% of the patients had a pheochromocytoma as the first manifestation constituting 45% of all patients with pheochromocytomas. The finding of a pheochromocytoma is a strong indication for a search for medullary thyroid carcinoma and for initiating family screening. (Henry Ford Hosp Med J 1992;40:276-7)

Pheochromocytoma is frequently asymptomatically associated with medullary thyroid carcinoma (MTC) in multiple endocrine neoplasia type 2 (MEN 2). Its clinical manifestations are usually subtle as more than 50% of patients are asymptomatic and normotensive (1,2). Using data of the Groupe d'Etude des Tumeurs à Calcitonine (GETC), French Medullary Study Group, we have evaluated the importance of pheochromocytoma presenting as the initial feature of MEN 2.

Material

At present, the GETC lists 113 families with hereditary MEN 2 and 66 apparently sporadic cases. Cases of pheochromocytoma were reported in 62 MEN 2A and in seven MEN 2B families. From the 62 MEN 2A families, seven have been excluded from this study because of lack of data. Sixty-six MEN 2 cases (33 MEN 2A and 33 MEN 2B) have been classified as apparently sporadic because no other cases had yet been found in their families. A pheochromocytoma was present in 28 of these 33 sporadic MEN 2A patients and in 14 of 33 MEN 2B patients. For patients presenting initially with a pheochromocytoma, the MTC diagnosis was made either concomitantly or subsequently (in five cases the diagnosis was made only by a stimulated calcitonin [CT] procedure).

Data

Incidence of pheochromocytomas as an initial presentation

Pheochromocytoma was the first manifestation in 35 of the 55 selected MEN 2A families (Table 1) (26 index cases and 19 relatives out of 99 MEN patients). The 20 other families without pheochromocytoma presenting first include 41 patients with pheochromocytomas. Among index cases, MTC was detected either clinically or biologically at the same time as or later than the pheochromocytoma, or by anamnesis of a patient with thyroid tumor.

The relatives who had pheochromocytoma(s) as first manifestations had already undergone adrenal surgery and were discovered by anamnesis of the index case during family screening; only a few had been tested for MTC after discovery of the pheochromocytoma. Pheochromocytoma was diagnosed either at the same time as the MTC or subsequently but never during the family screening for new cases.

In MEN 2B families, no patients were observed with pheochromocytoma as the initial presenting condition. In apparently sporadic MEN 2, 62% of the MEN 2A cases and 21% of the MEN 2B cases had pheochromocytoma as the initial manifestation. Table 2 shows the age at diagnosis of index cases in MEN 2A families and of apparently sporadic MEN 2A cases.

Discussion

In comparing all MEN 2A families, the proportion of pheochromocytomas is significantly higher in those families in which a pheochromocytoma was the initial manifestation in some member (64% versus 47%, $P < 0.01$).

A pheochromocytoma occurring as the initial manifestation appears to be a relatively frequent feature of MEN 2A; in the 35 MEN 2A families in which a pheochromocytoma occurred first in some affected member, 30% of the patients had a pheochromocytoma as the first manifestation, constituting 45% of all patients with pheochromocytomas. In apparently sporadic MEN 2A, 52% of the patients had pheochromocytomas occurring as the first manifestation.

A pheochromocytoma occurring first is rare in MEN 2B: no cases were observed in the MEN 2B families and in only one-fourth of the apparently sporadic MEN 2B cases did this occur. This is likely related to the ease of early diagnosis of MTC. Pheochromocytoma may occur in less aggressive diseases: the age of diagnosis in cases involving pheochromocytoma is older than the age of cases without it (20.5 versus 14.5 years, and age at

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Table 1
Number of Pheochromocytomas as the Initial Presenting Tumors in MEN 2A Families

	Families With Pheochromocytomas First (n = 35)	Families Without Pheochromocytomas First (n = 20)
Pheochromocytomas 1st	45	0
Total number of pheochromocytomas	99	41
Total patients	156	88

death 32.2 versus 19.3 years). The four patients with pheochromocytoma as the first manifestation were 16, 20, 24, and 26 years old at diagnosis. However, the age of discovery of pheochromocytoma is younger in MEN 2B than in MEN 2A.

Conclusion

The frequency of pheochromocytoma as the initial feature of MEN 2 must not be ignored; even unilateral pheochromocytoma may be an indicator of MEN 2. The presence of pheochromocytoma is an indication for the patient and the patient's relatives to be studied systematically for MTC as well as to be tested for von Hippel-Lindau and von Recklinghausen conditions.

The results presented here are a reflection of the evolution of improved screening procedures available during the past years. The practice of MTC detection when pheochromocytoma occurs and of pheochromocytoma detection when MTC occurs, using accurate means of diagnosis and family screening, will improve the prognosis in these patients and their affected relatives.

Table 2
Mean Age at Diagnosis for Index MEN 2A Cases

Appearance of Manifestations	MEN 2A Families Age at Diagnosis	Apparently Sporadic MEN 2A Age at Diagnosis
Pheochromocytoma 1st	42 yrs (n = 26)	44 yrs (n = 15)
MTC 1st, pheochromocytoma 2nd	32 yrs (n = 18)	33 yrs (n = 13)
Without pheochromocytoma	43 yrs (n = 11)	33 yrs (n = 1)

Pheochromocytoma is quite variably expressed in MEN 2A families and even in different branches of the same family. The factors responsible for this variable expressivity remain to be clarified.

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