Eur J Cancer Clin Oncol, Vol. 18, No. 7, pp. 645–650, 1982.
Printed in Great Britain.

0277-5379/82/070645-06$03.00/0

Familial Medullary Thyroid Carcinoma in Multiple Endocrine Neoplasia (MEN) IIa: Diagnosis and Problems in Treatment*

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Abstract—*A family with MEN IIa (medullary thyroid carcinoma (MCT), pheochromocytoma and hyperparathyroidism) was identified. Three relatives had been treated for MCT earlier. Eleven asymptomatic family members had elevated pentagastrin (PG)-stimulated serum immunoreactive calcitonin (i-CT) concentrations, including one who earlier had a pheochromocytoma removed. Nine of these subjects underwent thyroidectomy, and histological examination revealed multifocal MCT in all. Although surgery was judged complete in all, elevated PG-stimulated serum i-CT levels postoperatively indicated residual disease in 5. The natural history of MCTs in the present family varied, with most cases behaving benignly. Occasionally, however, the disease pursued an aggressive course. As MCT often metastasizes before being clinically evident, high cure rates can only be obtained by early diagnosis and treatment, possibly in the pre-metastasizing phase of C-cell hyperplasia, detectable only by elevated PG-stimulated serum i-CT levels.*

INTRODUCTION

MEDULLARY thyroid carcinoma (MCT) is a calcitonin-secreting neoplasm of the thyroid C-cells. The disease usually occurs sporadically but may be familial as an autosomal dominantly inherited disease. When familial, MCT is often associated with pheochromocytomas and parathyroid hyperplasia as a multiple endocrine neoplasia (MEN) IIa or associated with pheochromocytoma, Marfan-like habitus and multiple mucosal neuromas as a MEN IIb. Familial MCT develops through a multifocal hyperplasia of the C-cells, detectable only by elevated serum immunoreactive calcitonin (i-CT) determinations after provocative testing [1–3].

Because of the possible familial nature, screening of families of patients with MCT is generally advocated in order to identify and subsequently treat familial cases.

In an earlier investigation of families of patients with presumed sporadic MCT, we identified familial-occurring MEN IIa in two sibships, interrelated as first cousins [4]. This paper describes the results of an extended study of this family and emphasizes the difficulties in deciding how to treat affected family members in the light of the variable agressiveness of MCT in the MEN IIa syndrome.

Accepted 10 February 1982.
*This study was supported by grant 6/80 from the Danish Cancer Society.

MATERIALS AND METHODS

Probends in this family were two first cousins, treated at our institutions for MCT without prior recognition of this relationship. The family screening programme was gradually extended to include at least all persons older than 8 yr who were related by first degree to patients with MCT or pheochromocytoma. The investigation included physical examination, especially of the neck, blood pressure determination, analysis of a 24-hr urine collection for vanillylmandelic acid (VMA), epinephrine (E) and norepinephrine (NE), and blood sampling before (−5, −1 min) and after (+2, +5 min) an injection of pentagastrin (PG) (Peptavlon, Ayerst, 0.5 μg/kg body wt. diluted in 1–2 ml isotone sodium chloride given

intravenously within 5 sec). In these samples serum i-CT was determined by radioimmunoassay [5]. The detection limit was 20 pg/ml. Normal range for basal serum i-CT was 0–120 pg/ml. In twenty healthy controls the highest individually measured serum i-CT after PG stimulation as described above was 0–155 pg/ml. We therefore considered PG-stimulated serum i-CT concentrations exceeding 200 pg/ml as abnormally elevated values.

Serum concentrations of calcium, phosphorus and creatinine were measured in 37 subjects to detect possible hyperparathyroidism. Medical records of interest on living and deceased family members were obtained from private doctors and hospital archives.

Family members with elevated serum i-CT levels were hospitalized for further investigations, including routine blood tests, X-ray examination of the chest and trachea, thyroid and bone scintigrams, repeated 24-hr urinary collections for analysis of VMA, E and NE, and repeated determination of basal and PG-stimulated serum i-CT. When elevated serum i-CT levels were confirmed, thyroidectomy was performed if the subject accepted operation and no contraindications existed. During surgery the central neck and the accessible parts of the upper mediastinum were explored for enlarged lymph nodes which, if present, were removed.

Postoperative basal and PG-stimulated serum i-CT levels were determined at least 4 months after surgery.

RESULTS

The pedigree of all investigated, and of deceased family members of interest, is shown in Fig. 1.

In addition to the two first cousins, who were the probends in this family, two other relatives had formerly been treated at other institutions for MCT and pheochromocytoma respectively. Information on the clinical disease course in these four patients is given in Table 1.

Among 6 deceased family members, clinical information was accessible in four. They had died between 56 and 80 years of age, without clinically evident thyroid cancer or pheochromocytoma. Autopsies were not performed.

The present investigation disclosed elevated PG-stimulated serum i-CT levels in 11 asymptomatic family members, including the patient formerly treated for pheochromocytoma. Levels of serum i-CT, results of physical neck examination, operative findings and postoperative levels of serum i-CT in these 11 subjects are shown in Table 2. In only one of these family members was basal serum i-CT within

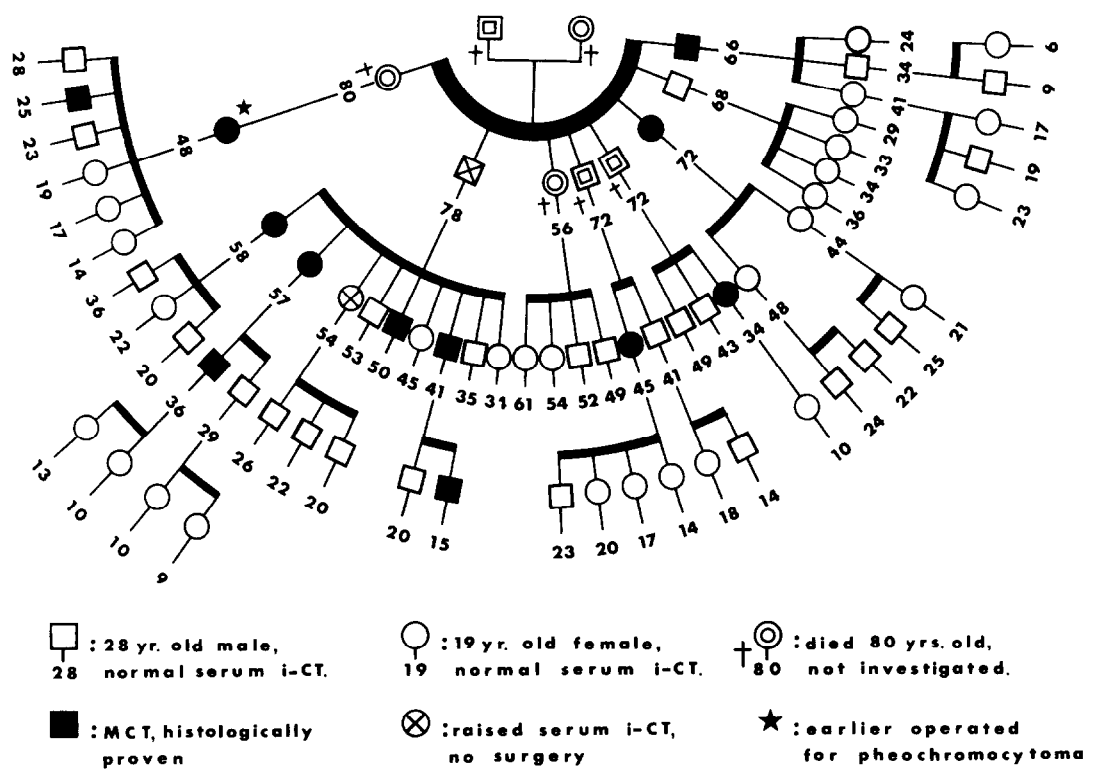

Fig. 1. Pedigree of investigated members of the family with inherited MEN IIa. Normal serum i-CT indicates normal basal and pentagastrin-stimulated serum immunoreactive calcitonin levels.

Table 1. The clinical disease history in 4 patients with previously unrecognized familial MEN IIa

Female, 59 years old. Probend. In 1953 right hemithyroidectomy for solid thyroid tumour with eosinophilic ground substance (MCT). In 1969 left hemithyroidectomy and left radical cervical lymph node dissection (in two operating procedures) for MCT with lymph node metastases. Serum i-CT (1979) basal: 40; PG-stimulated: 1400.

Female, 34 years old. Probend. In 1974 left hemithyroidectomy with radical left cervical lymph node dissection in two operating procedures for MCT with lymph node metastases. Postoperative unilateral recurrent laryngeal-nerve injury. Serum i-CT levels in 1979 basal: 340; PG-stimulated: 900. Underwent subsequent right hemithyroidectomy for multifocal MCT. Postoperative serum i-CT levels basal: 70; PG stimulated: 1300.

Male, 40 years old. MCT diagnosed by thyroid biopsy in 1977. Metastases in cervical and in mediastinal lymph nodes. Radio- and chemotherapy produced some initial regression. Now progressive disease with metastases in bone, one testis and associated watery diarrhoea. Basal serum i-CT: 42,000 and increasing.

Female, 48 years old. In 1966 severe hypertensive crisis with pulmonary oedema followed by profound hypotension immediately after gynecological surgery (bilateral Fallopian tube resection). A diagnosis of pheochromocytoma in the left adrenal gland was subsequently made, and adrenalectomy performed. At the present investigation raised serum i-CT levels.

Upper normal limits for serum immunoreactive calcitonin (i-CT) are basal: 120 pg/ml; pentagastrin (PG)-stimulated: 200 pg/ml.

the normal range, although at the upper normal limit. In one subject with later surgically proven MCT, physical examination of the neck and thyroid scintigram revealed no abnormality. None of the subjects showed evidence of distant metastases by general physical examination, X-ray of the chest and bone scintigrams. None of the subjects had diarrhoea, flushing or ectopic Cushing syndromes.

Nine of these eleven subjects with raised serum i-CT levels underwent subsequent thyroidectomy. During surgery cervical or upper mediastinal lymph-node metastases were disclosed in 3 and, although surgery was judged complete, serum i-CT did not decrease to normal values postoperatively in these subjects. Among six subjects with MCT seemingly confined to the thyroid gland, postoperative serum i-CT levels decreased to normal values in four, whereas elevated basal and/or PG-stimulated values postoperatively were found in two. Neither the age nor the magnitude of preoperative serum i-CT in these nine subjects correlated with the ability to restore serum i-CT to normal levels by thyroidectomy. Histological examination of all thyroid glands

Table 2. Information on all family members in whom MCT was suspected due to elevated pentagastrin stimulated-(PG-stim.) serum immunoreactive calcitonin (i-CT) levels

Sex	Age	Preoperative serum i-CT (pg/ml) Basal (< 120)	PG-stim. (< 200)	Clinically evident thyroid tumour	Lymph node metastases at surgery	Postoperative serum i-CT pg/ml Basal (< 120)	PG-stim. (< 200)
♀	48	5600	37000	+	+	2100	26500
♂	25	1800	24000	+	−	180	800
♂	78	12500	—	+	no surgery, advanced age	—	—
♀	57	550	3000	+	−	< 20	70
♂	36	130	1430	−	−	70	65
♀	54	190	650	(+)	no surgery, heart disease	—	—
♂	50	9500	320000	+	−	< 20	< 20
♂	15	460	2800	+	+	575	3200
♀	45	2500	16800	+	−	20	240
♀	72	5300	—	+	+	1550	—
♂	66	1050	10500	+	−	< 20	25

The values for i-CT written in parantheses indicate the upper normal limit. The order of the family members corresponds to reading the pedigree (Fig. 1) from the left, following each family branch down through the generations.

removed showed multifocal MCT, the smallest tumours (up to a size of 3×3×3 mm) being found in the subject with high normal basal serum i-CT levels. Surgical complications amounted to one unilateral recurrent laryngeal-nerve injury. In two subjects with raised serum i-CT levels, surgery was not undertaken due to advanced age and a severe heart disease respectively.

Determination of 24-hr urinary excretion of VMA, E and NE did not raise suspicion of pheochromocytoma in any family member. All of 37 initially investigated persons had normal levels of serum calcium and phosphorus, so further screening for parathyroid hyperfunction was omitted. Subsequently, the subject with suspected MCT and a heart disease had developed slightly elevated serum calcium and parathyroid hormone levels. None of the investigated family members had mucosal neuromas.

DISCUSSION

This investigation identified a family with multiple cases of dominantly inherited MCT. A symptomatic pheochromocytoma had earlier been removed in one of the family members, but no new cases were identified. Hyperparathyroidism was not initially found, but later became suspected in one subject with probable MCT. None had mucosal neuromas. The familial disease could subsequently be classified as a MEN IIa, although with a low prevalence of pheochromocytomas and hyperparathyroidism compared to most reported families [1–3, 6–9].

Based on elevated basal and/or PG-stimulated serum i-CT levels, thyroidectomias for MCT were performed in 9 subjects. In one of these, elevated serum i-CT levels were the only abnormality preoperatively found, in agreement with the concept that serum i-CT levels are the most sensitive diagnostic criterion for MCT. In all thyroid glands removed MCT was multifocal, as is the case with the familial variety of this disease [1–3, 6, 10]. Although surgery was judged complete in all operated subjects, postoperatively elevated basal and/or PG-stimulated serum i-CT levels gave evidence of residual disease in 5. The validity of this assumption is supported by the sensitivity and high degree of specificity of serum i-CT levels as preoperative tumour markers for MCT. Further support has been provided in studies where second operations in patients with clinically undetectable residual disease but elevated serum i-CT levels invariably disclosed MCT deposits [11, 12].

During surgery only enlarged lymph nodes were removed. The finding of elevated serum i-CT levels in 5 out of 9 subjects postoperatively could suggest that a more extensive operating procedure with routine cervical [1] and upper mediastinal lymph node dissections [13] should have been performed. However, when metastases in cervical lymph nodes are present, even an extensive operating procedure usually fails to achieve surgical cure [10–12].

As expected when the investigation of this hitherto unrecognized family was initiated, MCTs were thus disclosed in variable, but often advanced, stages of development. The pre-metastasizing C-cell hyperplasias were not detected, perhaps explainable by the fact that no family member had the combination of normal basal and only slightly elevated PG-stimulated serum i-CT levels. A possible lack of sensitivity and specificity of our CT-assay could, however, contribute to this finding.

With refined CT-assays and regular control of family members at risk, detection of C-cell neoplasias in the hyperplastic stage has been accomplished by several groups [1–3]. Complete eradication of the C-cell neoplasias by thyroidectomy in this stage has seemingly invariably been achieved, as judged from normal postoperative levels of PG-stimulated serum i-CT [1–3]. When MCT, even clinically undetectable, has developed, the results of thyroidectomias are impaired as the tumour by then has often spread beyond the thyroid gland [1, 3, 9]. When the thyroid tumour is clinically evident, as in most subjects in the present series, the chance of cure deteriorates further [3, 6]. This correlation between the histopathological stage of the thyroid C-cell neoplasms and the results obtained by surgery emphasizes the importance of early detection of this disease.

Eradicating thyroid C-cell disease does not, however, necessarily implicate the achievement of a permanent disease-free state. Calcitonin-containing cells are also found outside the thyroid gland [14] and could be identical to the thyroid C-cells, thereby invalidating thyroidectomy as a means of preventing C-cell neoplasias in patients with MEN IIa [15, 16]. The ability to invariably restore serum i-CT levels to normal values by thyroidectomy in patients with thyroid C-cell hyperplasia [1–3] seems to indicate that extrathyroidal development of primary C-cell neoplasms rarely occurs, but only long-term follow-up on these patients could clarify this question.

Even convinced that surgical cure for genetic C-cell neoplasias can be obtained if the disease

is detected and treated in an early stage, is then an active treatment policy against MCTs in the MEN IIa syndrome justified? In the present family, several members have reached old age harbouring asymptomatic MCTs, even with cervical lymph node deposits. Furthermore, 3 persons who had died at rather old ages from other causes must have had MCT as this disease occurs in some of their children, and the penetrance is usually complete when PG-stimulated serum i-CT levels are used as tumour markers [3]. One patient had no clinically detectable disease 28 and 11 years after right and left hemithyroidectomias respectively, although slightly elevated but stable i-CT levels had been found during the last 3 years, giving evidence of residual disease. On the other hand, the disease runs an unpredictably more malignant course in occasional family members as exemplified by the 40-yr-old man with progressively increasing serum i-CT, metastases in mediastinal lymph nodes, testis and bone, associated pain and watery diarrhoea. The disease course is thus extremely varied, as in other families [8, 9, 13, 17, 18]. Fatal cases have, however, occurred in the majority of reported families [1, 6, 9, 10, 19]. Omitting cases of hereditary MCT recognized only by screening for elevated serum i-CT, Block *et al.* [6] found that the average age of death for patients with MEN IIa was 44 yr and 50 yr in families with and without concomitantly occurring pheochromocytomas respectively. The prognostic outlook for affected subjects in other families, including the present, seems somewhat more favourable [2, 8, 6], pointing to differences in the biological behaviour of MEN IIa between families [16]. Comparisons are, however, difficult due to the variability within families. Factors determining the biological behaviour of the disease have not hitherto been discovered [13], and selection of subjects in high risk of an aggressive clinical course of MCT is therefore impossible.

Recognizing the variable but occasionally aggressive biological behaviour of familial MCT in MEN IIa, 6 different medical groups [1–3, 6, 7, 9–13, 19–21], caring for in all 30 families, advocates an aggressive approach with early diagnosis and treatment. More conservative views have, however, been expressed [15, 17], stressing the importance of taking the biological behaviour of MCT in the particular family in question into account [16, 18].

If a non-interfering policy towards familial MCT is adopted many subjects would be spared unnecessary thyroidectomias, but the occasional and unpredictable malignant disease course in some subjects would not be prevented. An intermediate aggressive approach to these families, performing thyroidectomy when a thyroid tumour is clinically evident [16] or when basal serum i-CT has reached a certain high level [17], seems to us to have little justification. Aggressive tumours would probably have metastasized by then, and most non-aggressive tumours will probably become clinically evident with age, as in all affected elderly subjects in the present family. Perhaps young age, when initial abnormalities in serum i-CT levels develop, could be indicative of a more aggressive biological behaviour. Moreover, the development of a slow-growing malignant tumour is more hazardous in younger individuals with a longer life expectancy. Reconsidering our approach to the present family, we thus do not judge the thyroidectomias performed in the 72 and 66-yr-old family members necessary.

Even if a non-interfering policy towards familial MCT is adopted, investigations for the familial nature of MCT cannot be spared. Besides the aggressive clinical course in the 40-yr-old man described above, the spontaneous clinical course in 3 patients with familial disease lead in consequence to multiple thyroid surgery in two, with a recurrent laryngeal-nerve injury in one and a life-threatening hypertensive crisis from a pheochromocytoma in the third. With awareness of the familial nature of the disease, proper thyreoidectomy can be undertaken if surgical treatment of MCT is decided upon. In every case, family members at risk should be regularly controlled for pheochromocytomas which, when detected, must be removed [1, 2, 16].

In the MCT-mucosal neuroma syndrome (MEN type IIb) the thyroid neoplasm is definitely malignant, and measures to early diagnosis and to subsequently thyroidectomize these patients is a necessity [22].

In conclusion, the present family demonstrates a usually benign but occasionally and unpredictably aggressive clinical course of MCT in the MEN IIa syndrome. We consider that thyreoidectomy, in experienced hands, can be performed with a small surgical risk and with no serious impairment of quality of life, whereas living with a thyroid tumour that may occasionally become malignant will cause anxiety and perhaps have a lethal outcome. In an attempt to cure the disease we will therefore adopt an active treatment policy towards family members who develop elevated PG-stimulated serum i-CT levels before the age of 40–50 yr, whereas a primarily conservative approach will

be adopted with older individuals. All adult family members have received written information on genetic and clinical aspects of the disease. We offer regular control of basal and PG-stimulated serum i-CT levels and of 24-hr urinary VMA, E and NE excretion in individuals older than 8 yr at risk, starting off with basal serum i-CT determination in children from the age of 5 yr. Measures to improve our calcitonin radioimmunoassay have been undertaken in order to be able to detect C-cell hyperplasias. In our opinion the disease has not such a severe impact on life that advice against child-breeding is justified.

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