The genetic aspects of medullary thyroid carcinoma: recognition and management

ABSTRACT—*Objective:* to examine the extent to which clinicians recognize the genetic aspects of medullary thyroid carcinoma (MTC) and undertake appropriate investigation and management of patients and their at-risk relatives.
***Design:* retrospective review of case notes.**
***Subjects:* all individuals aged 70 or under with a 'raised' calcitonin level during 1990-91. Information was obtained from a questionnaire. Forty-one cases were diagnosed in 1990–91: 10 (24%) multiple endocrine neoplasia (MEN) type 2A, four (10%) MEN type 2B, and 27 (66%) sporadic MTC. Between 1980 and 1989, 87 cases were diagnosed: 20 (23%) MEN type 2A, six (7%) MEN type 2B, four (5%) familial MTC, 53 (61%) sporadic MTC, and four (5%) of uncertain diagnosis.**
***Main results:* a pedigree was drawn in only 7/37 (19%) and 26/83 (31%) of cases diagnosed in 1990–91 and 1980–89, respectively, where a family history had been taken. All known hereditary cases were investigated for phaeochromocytoma. In 9/27 (33%) and 14/52 (27%) apparently sporadic cases diagnosed in the two periods respectively, no investigations were performed. Genetic counselling was offered to all known hereditary cases except one, but no offer was made in 11/25 (44%) and 16/52 (31%) apparently sporadic cases. There was no record that screening should be offered to the family in 15/35 (43%) and 25/68 (37%) cases identified from clinical investigations; in the majority it could be argued that it should have been.**
***Conclusions:* this study has shown that clinicians do not always have the necessary training or experience to undertake family studies and screening in this rare disorder.**

Although single gene disorders are mostly rare, there are many thousands of them. All doctors will thus encounter diseases with an important genetic component, but they may not always realise that they have done so or be aware of the correct management.

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Medullary thyroid carcinoma (MTC) is characteristic of such disorders. It occurs as a sporadic tumour and as a component of the dominantly inherited cancer syndrome, multiple endocrine neoplasia (MEN) type 2 [1], subdivided as follows:

- MEN type 2A: the commonest type of MEN type 2, comprising MTC, phaeochromocytoma and occasionally hyperplastic parathyroid glands
- MEN type 2B, in which there are associated developmental abnormalities, especially of the enteric nerve plexuses; it affects the thyroid and adrenal glands but not the parathyroid; on average, tumours are present at younger ages and may be more aggressive
- familial MTC: found in large families in which this tumour is the only abnormality; it is possibly a more indolent form of the disease.

The rarity of this syndrome does not prevent devastating consequences for affected families. Early recognition by appropriate calcitonin screening permits prevention in family members [2], and recent developments have made a precise DNA diagnostic test available [3].

The aim of the enquiry reported here was to assess the extent to which clinicians recognise the genetic aspects of cases of MTC and MEN type 2 and undertake appropriate investigation and management of the patients and their at-risk relatives.

The following standards for diagnosis and management were adopted:

1. *Family history*: a full family history should be taken, at least out to second-degree relatives, and the pedigree drawn.
2. *Surgery*: in any case of MTC where heritable disease is a possibility, surgery should include removal of both thyroid lobes because of the probability of multifocal disease.
3. *C-cell hyperplasia*: the assessment of C-cell hyperplasia in a thyroid resected from an apparently sporadic case of MTC is of great importance since it is suggestive of familial disease.
4. *Investigation for phaeochromocytoma*: once the diagnosis of MTC has been made, screening for other components of hereditary disease such as phaeochromocytoma should be undertaken.
5. *Family screening*: because of the incomplete penetrance of the MEN type 2 mutations and the possibility of new mutations, a negative family history cannot completely exclude heritable disease.

Biochemical screening by measuring calcitonin levels after a stimulation test (using pentagastrin or calcium), rather than just the basal calcitonin level, should be offered to family members in any case where there remains even a small possibility of heritable disease [4].

6. *Genetic counselling and DNA testing*: since the discovery of the MEN type 2 gene in 1993, the first step in assessing relatives of a known hereditary case is to test DNA from an affected family member for mutation in the proto-oncogene *RET*. DNA testing of apparently isolated cases may also help establish the presence of heritable disease. Information about the possible inherited risks, DNA testing, biochemical screening and prophylactic surgery, should be made available to all family members potentially at risk.

These standards are described in more detail in the full report of the Royal College of Physicians (RCP) to the Department of Health [5] (available on request from the RCP).

Methods

The criteria for ascertainment in this study included all individuals aged 70 years or under at the time of measurement who had a 'raised' calcitonin (basal or stimulated level) during 1990–91 reported by six regional immunoassay centres covering England, Wales and Scotland. The reference laboratories did not use a standardised assay method and had different criteria for what constituted a 'raised' calcitonin. For the purposes of this study, these assay cut-off points were increased slightly to exclude borderline cases (Table 1).

Information was obtained from a questionnaire distributed in September 1993, and completed either by the clinician who requested the calcitonin test (usually a consultant surgeon or a consultant in general medicine) or by a member of the enquiry team if the clinician had managed more than five cases.

The success of this enquiry depended on the assurance that information about patients, their families, professionals and hospitals would remain confidential. Office procedures to ensure confidentiality were adopted during the study, and included separate password-protected databases for questionnaire data and identifying details, linked only through a unique number assigned to each case. At the time of publication of the findings, all case identifying details will be destroyed.

Table 1. Calcitonin assay cut-off points used for study

Laboratory	Definition of 'raised' calcitonin	
1	Basal: >300 ng/l	Stimulated: ≥2½ times basal reading
2	Basal: >45 ng/l	Stimulated: >135 ng/l
3	Basal: >110 ng/l	Stimulated: >220 ng/l
4		Stimulated: >300 ng/l
5	Basal: >100 ng/l	
6		Stimulated: >27 pmol/l

Results

Cases were excluded if they had a raised calcitonin assay but no diagnosis of MTC had been made. Information could not be sought in nine cases since insufficient details were available from the laboratory to identify the individual and/or clinician.

The questionnaire was distributed for 212 of the patients diagnosed as having MTC who were aged 70 or under during 1990–91. It was completed for 157 patients. Of the 55 cases for whom the questionnaire was not returned, the notes were untraceable (13 cases) or the clinicians stated that they did not wish to participate in the study (11). No reason was given in 31 cases, despite sending a reminder. There was no further follow-up for these 55 cases. The possibility of response bias could not be investigated in this study due to the lack of information on cases where a questionnaire was not completed.

This article describes 41 cases where the diagnosis was made during 1990-91 (following a raised calcitonin level in this period), and 87 cases diagnosed between 1980 and 1989 (but whose raised calcitonin assay in 1990–91 led to ascertainment in this study). The remaining 27 cases diagnosed prior to 1980 and two cases diagnosed during 1992 are excluded from the analysis.

The final diagnoses of the 41 cases diagnosed in 1990–91 and the 87 cases diagnosed between 1980 and 1989 are shown in Table 2. In one apparently sporadic case the questionnaire was sent to a consultant who had been asked by a colleague for a second opinion,

Table 2. Final diagnoses of cases during two periods of ascertainment, 1990–91 and 1980–89

	Years			
	1990–91 (*n*=41)		1980–89 (*n*=87)	
Final diagnosis	No.	%	No.	&
MEN type 2A	10	24	20	23
MEN type 2B	4	10	6	7
Familial MTC	—	—	4	5
Sporadic MTC	27	66	53	61
Uncertain	—	—	4	5

MEN = multiple endocrine neoplasia
MTC = medullary thyroid carcinoma

but insufficient details were available for this enquiry and the case was excluded from further analysis.

Table 3 gives the proportion of cases which met the appropriate standards of diagnosis and management. Genetic counselling, when provided, was by a clinical geneticist in 5/13 (38%) and 11/27 (41%) known 'hereditary' cases in 1990–91 and 1980–89, respectively, and in 5/13 (38%) and 15/34 (44%) apparently sporadic cases in 1990–91 and 1980–89, respectively.

There were 15 cases identified from clinical investigations in 1990-91 where no screening was offered to the family, for the following reasons:

- patient disowned by parents (1 case)
- no family members at risk (2)
- the clinician seems to have been aware of the issue of family screening but to have left it to someone else (4)
- the clinician had no policy about screening relatives of apparently sporadic cases (6)
- the policy was based on assumptions (lack of evidence of C-cell hyperplasia, index cases diagnosed over the age of 40 years) that are reasonable but not generally agreed to be best practice (2).

Of 25 similar cases diagnosed between 1980 and 1989 no screening was offered to the family because:

- the patient was adopted (1 case)
- there were believed to be no family members at risk or none in the UK at the time (5)
- the clinician had no genetic screening policy (1)
- the policy was based on reasonable assumptions (see above), but not generally agreed to be best practice (15)
- no reason was given for the lack of screening (3 cases, aged 18, 36 and 36 years at diagnosis).

Clinicians were also asked about screening of at-risk relatives, with the following results:

- 31/67 (46%) consultants who would normally discuss with the patient the possibility of screening family members at high risk had never referred these patients to a geneticist
- 20/50 (40%) consultants were unsure about the age at which to commence calcitonin screening of children of a known MEN type 2 patient
- 13/40 (33%) consultants reported *basal* calcitonin measurement as the method for screening the children of a known MEN type 2 patient
- only one of the 50 consultants who stated that they had carried out screening procedures for high-risk relatives indicated that they would not screen descendants of the head of an apparently unaffected branch who had a normal pentagastrin test at age 40 or above; seven consultants gave higher ages, five younger and 37 did not state a policy based on pentagastrin stimulation test results
- 33/73 (45%) consultants did not know whether DNA diagnosis for MEN type 2 was available.

Discussion

Potential sources of bias

The validity of the conclusions to be drawn from these results depends in part on the representativeness of the cases for which data were available. For this reason, potential sources of bias are discussed further.

Data from the Thames Cancer Registry suggest an incidence of 60–80 cases of MTC each year in the UK [1,2]. Registration of cases with the Office of Population Censuses and Surveys (OPCS) for 1987–89 suggests about 40 new cases annually in England and Wales, with less than 35 cases aged 70 or under. This discrepancy may be due to overestimation from the Thames data or under-reporting to OPCS in other regions.

Including cases where the notes were untraceable or the questionnaire not returned, the method of ascertainment used in this study could have identified 69% of cases diagnosed in 1990–91 in England and Wales based on OPCS estimates. Cases presenting with a lump in the neck, which is then removed, would subsequently have low calcitonin levels and would not have been identified by this method. Management of these cases is not expected to differ substantially from those presented in this study.

Since questionnaires are less likely to be completed for cases where standards were not met, the results presented here may overestimate the proportion of cases where standards *were* met, but this potential response bias could not be assessed.

Patients found to have raised calcitonin levels during 1990–91 included those first diagnosed between 1980 and 1989 who survived until 1990–91, as well as incident cases during 1990–91. The former group is only the *subset* who survived until 1990 of all the cases diagnosed between 1980 and 1989. The percentages quoted may not therefore be directly comparable for the two groups due to this bias in ascertainment.

The need for wider expertise in genetics among clinicians

This study has shown that clinicians do not always have the training or experience to undertake family studies and screening in this rare disorder. All families who might have this syndrome should be reviewed by a team having the necessary skills and experience, given the complexity of screening and diagnosis. This disorder is typical of many genetic disorders where family members remain at risk for years and require systematic follow-up. This need is familiar to clinical geneticists who have established genetic registers in

Table 3. The proportion of cases which met standards of diagnosis and management

Standard	Cases diagnosed in: 1990–1 No.	%	1980–89 No.	%
Family history taken and recorded:	37/40	92	83/84	99
If 'yes', pedigree drawn in notes	7/37	19	26/83	31
If 'yes' and positive for MTC, identification through family screening	6/8	75	14/17	82
Investigated for phaeochromocytoma:				
Known 'hereditary' cases	14/14	100	30/30	100
Apparently sporadic cases	18/27	67	38/52	73
Subsequent completion surgery following partial thyroidectomy	6/8	75[1]	24/26	92[2]
Comment on C cell hyperplasia in first thyroid histology report:				
Apparently sporadic cases	6/20	30	6/38	16
Record of offer of genetic counselling:				
Known 'hereditary' cases	13/14	93[3]	27/30	90[4]
Apparently sporadic	14/25	56	36/52	69
Record that screening should be or had been offered to the family of cases identified from clinical investigations	20/35	57	43/68	63

NB: 'Hereditary' denotes a diagnosis of MEN type 2A , MEN type 2B or familial MTC.

1 Thyroidectomy not subsequently completed in two cases, due to infiltration of the trachea

2 Thyroidectomy not subsequently completed in two cases: one where surgery was performed 'by a surgeon unused to MTC', another where the patient was reported to be unfit and unwilling

3 No counselling recorded in one case where all relatives were dead and the patient had no children

4 No counselling recorded in one case as the patient was adopted, in one where the patient had no relatives in the UK, and in one where the consultant reported they were 'hoping to organise genetic counselling'

MEN = multiple endocrine neoplasia

MTC = medullary thyroid carcinoma

the UK designed for the long-term follow-up of family members who may have inherited a pathological mutation: for example, Huntington's disease, Duchenne muscular dystrophy, adult polycystic kidney disease and myotonic dystrophy, each of which has mutations which can be sought in family members. When found, they provide opportunities for counselling, reproductive decision making and prenatal diagnosis—but not yet for treatment. However, an increasing number of cancer syndromes like MEN type 2 (and including breast, ovary and bowel cancer) which have an identifiable genetic component can be prevented or treated effectively if recognised early.

These disorders normally present to—and are managed by—clinicians who do not have specialist genetic knowledge, and existing genetics clinics will not be able to cope with all these cases. If new genetic knowledge is to be used effectively, some new mechanisms must be found to integrate genetics into the practice of the widening circle of clinicians to whom it will be relevant. Continuity of monitoring and of care is required and must therefore involve the primary care team.

Recommendations

The main recommendations are as follows:

Family history taking: the family history should be taken at least out to second-degree relatives, and the pedigree drawn. Hospital records and death certificates should be pursued for relatives who might be affected, paying particular attention to the presence or absence of C-cell hyperplasia, phaeochromocytoma, parathyroid disease or physical abnormalities.

Genetic counselling and DNA testing: genetic counselling should be offered by individuals who are familiar with the details of MTC, including the issues arising from incomplete penetrance, and who also have the necessary counselling skills and experience. Communication should include a detailed letter to the patient, copied to the patient's general practitioner. Such a letter acts as a permanent record, and allows the patient to inform other members of the family.

Mutation analysis should be available from a molecular genetics laboratory familiar with the appropriate DNA diagnostic test.

Criteria for screening at-risk relatives: the criteria for initiating screening in relatives should be clearly defined, including the ages at which screening should begin and when negative screening can be assumed to indicate minimal risk for the individual and descendants.

Laboratory methodology: it is essential that precise methodology be defined, including thresholds for identifying 'screen positive' and optimum means for stimulation (eg pentagastrin).

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