Register of Multiple Endocrine Neoplasia Type 2 Syndromes in the United Kingdom

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A collaborative group for the study of multiple endocrine neoplasia type 2 (MEN-2) syndromes comprised of clinicians and laboratory scientists has been set up in the United Kingdom. Its aims are 1) to provide a basis for collaborative work on MEN-2; 2) to establish a register of patients; 3) and specifically to conduct studies aimed at defining the best policy for screening the families of apparently sporadic patients, to establish radioimmunoassays for family screening, and to identify large kindreds for genetic linkage studies using DNA polymorphisms.

In 1982, a study group for medullary thyroid carcinoma (MTC) was set up in the United Kingdom to facilitate clinical and laboratory studies of MTC and MEN-2 by providing a forum for dissemination of information and by making clinical material available. The group has set up a register of patients with familial MEN-2 and of patients with apparently sporadic MTC.

More specific projects have also been initiated: 1) determination of the best screening policy for first-degree relatives of apparently sporadic index cases; 2) a calcitonin, katacalcin, and calcitonin gene-related polypeptide (CGRP) radioimmunoassay specifically for family screening within the group; and 3) ascertainment of large families and collection of lymphocytes for DNA extraction to be used in linkage studies with DNA polymorphisms.

At present, the group has 53 participating members in the United Kingdom and eight European countries, as well as contributors from Hong Kong and the United States. They include endocrinologists, surgeons, pathologists, clinical geneticists, cytogeneticists, medical oncologists, radiotherapists, and cell and molecular biologists.

The MTC/MEN-2 Register

Ascertainment

All clinical members of the group were asked to provide details of cases with MEN-2 or apparently sporadic MTC under their care, including patients who had died within the past five years. For each patient, information collected includes a family pedigree and minimal data on each family member (name, alive or dead, dates of birth and death, whether affected, and if not, whether screened). For each affected individual (MTC or pheochromocytoma), the information includes details of age at onset, age at diagnosis, mode of diagnosis (clinical or screen), findings at surgery, pathology, and evidence of parathyroid involvement and of congenital abnormalities.

Confidentiality

One objective of the Register is to extend the family pedigrees for linkage studies in order to determine if apparently distinct families are in fact related. However, no information is made available which can be linked to identifiable individuals, and no approach to any patient or family is permitted except with written permission of the clinician who contributed the information originally. Obtaining the informed consent of individuals to be included on the Register is the responsibility of the clinician in charge of their care and of local ethics committees; as a rule, consent has been obtained, and patients have been enthusiastic and extremely helpful with the family studies.

Results

To date, 101 index patients have been reported, of whom 24 are in known apparently distinct MEN-2A families; four are in families suspected on the basis of screening results; and 10 are MEN-2B (two who are known to be familial). The rest are apparently sporadic cases. This figure may represent possibly 20% of the
MEN-2 families in the United Kingdom. More complete ascertainment may shortly be possible through central cancer registry records which will list, variously, all known cases of MTC (sporadic or familial), all patients with both MTC and pheochromocytoma, all cancers in first-degree relatives of patients with MTC for a large cohort aged 0-16 years in 1939, and all cases of MTC diagnosed under age 15. We are already aware of several large MEN-2A families not under the care of members of the group.

The Uses of the Register

Data for age at onset and screening policy

There are three categories of data: 1) age at estimated clinical onset; 2) ages at which otherwise unsuspected cases are detected by initial screening; and 3) ages at which individuals with a previously negative screening test convert to positive. Data on conversion by the screening test will require a lengthy prospective study (1) but eventually will determine the age at which screening of at-risk individuals can be discontinued. Data on the age at clinical onset and the age at which individuals are detected on first screening can be collected more quickly in order to estimate individual risk within a known family and to estimate risk (hence, decisions about screening) in the relatives of apparently sporadic cases.

For example, in the family shown in the Figure, the risk to the siblings of the index patient (II-1 and II-2) will include a component of prior genetic risk (determined by the fraction of MTC that is familial and how this risk is modified by the age at which the parents are clinically unaffected) and a component of age-related conditional risk (if they are well at age 50, their risk is less than if they were 20). Similarly, the children of the index case (III-1 and III-2) will have a prior genetic risk as above (but increased by the possibility that their father is a new mutation to the inherited form) and an age-related conditional risk. Using rough estimates of genetic risk (eg, 25% of all cases of MTC are familial), we can already use age-at-onset data in known families to provide an estimate of individual risk, taking into account age-related and genetic factors (Figure). This may serve as a guide to select individuals for screening.

We need better information, however, on which to base estimates of the proportion of familial to truly sporadic cases, the change in this proportion at different ages of clinical onset (this would modify the one-fourth prior genetic risk assumed in the Figure), and the proportion of “sporadic” cases at each age which are new mutations. Two other group studies may help to provide this information. The first study is a systematic screening of all first-degree relatives below the age of 65 years of apparently sporadic index cases. Registration of all these families not only will allow us to pool the information from several centers but also will provide the means of long-term follow-up, so that the truly sporadic cases can be identified with increasing accuracy. The second study is a prospective evaluation of C-cell hyperplasia in a parasagittal slice of all thyroids resected for tumor in the United Kingdom in a single year. The primary purpose is to define the procedure and criteria for diagnosis of C-cell hyperplasia, but the study will also provide a cohort of patients who can be followed by family screening and data on the incidence and age distribution of inherited and sporadic forms and of new mutations.

Figure

Pedigree with an apparently sporadic case of MTC (II-3)

The risk to the siblings of the index case (II-1 and II-2) can be estimated along these lines: assume 1/4 of all MTC are of the heritable type (making no adjustment for the age of presentation). Then the probability that one or the other parent of the index case was a carrier is 1 in 4, and the prior genetic risk to their children, II-1 and II-2, is in each case 1/4x1/2 = 1/8. But, each is apparently unaffected at the age of 50. From the age at onset data (not shown), 80% of gene carriers have clinically manifest disease by age 50. Therefore, the prior genetic risk is modified by an age-related conditional risk as follows:

<table>
<thead>
<tr>
<th>Probability that:</th>
<th>carrier</th>
<th>not carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior genetic</td>
<td>1/8</td>
<td>(1 - 1/8)</td>
</tr>
<tr>
<td>Conditional age-related</td>
<td>1/5</td>
<td>1</td>
</tr>
<tr>
<td>Multiplied =</td>
<td>1/40</td>
<td>35/40</td>
</tr>
</tbody>
</table>

Combined risk that II-1 or II-2 is a carrier = \( \frac{1/40}{35/40} = \frac{1/36}{35/40} \)

These estimates could be further refined by additional data, as described in the text.
Genetic studies
The Register is the starting point to identify large pedigrees for linkage studies. Furthermore, it will provide widely-based information on the possible heterogeneity of MEN-2 syndromes: the distinctness or otherwise of MEN-2A and -2B, association with other endocrine or presumed neuroectodermal tumors and congenital abnormalities, and the incidence of the different components of the syndrome in different families. Evidence will be sought also for phenomena such as premutation and parental age effects.

The possibility of an international register was discussed at the First International Workshop on MEN-2 held in Kingston, Ontario in June, 1984. It is likely that, as the circle of contributors enlarges, the ability to verify and complete the data will diminish, while the risk of accumulating a large amount of poorly focused and possibly unreliable information will increase. It may be more effective to use successive workshops to collate and examine data from different groups on specific questions. Data could either be analyzed and circulated to contributors before the meeting or presented and analyzed at the workshop itself. In that way, all contributors would have the opportunity to participate in the analysis and discussion of their data in relation to the whole.

Reference