Familial Nasopharyngeal Carcinoma in a Cohort of 200 Patients

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Objectives: To describe the characteristics of familial nasopharyngeal carcinoma (NPC) in a high-risk population and to determine the role of screening first-degree relations.

Design: An analysis on a cohort of 200 patients newly diagnosed as having NPC.

Setting: A tertiary-level institution.

Patients: The patients were divided into 2 groups. Patients in group 1 had a first-degree relative with NPC, and those in group 2 did not. For patients in group 1, the relationship and the time interval between affected relatives were noted. The clinical and pathological factors of the 2 groups were obtained and statistically analyzed.

Results: There were 15.5% of NPC patients who had an affected first-degree relative. Of the affected relatives, 71% were siblings and 29% were parents. The mean interval between affected siblings was 5.3 years, while that between an affected parent and a child was 24.5 years. No differences were noted in the clinical factors between familial and nonfamilial NPC patients. Most patients in both groups were diagnosed as having stage III or IV NPC.

Conclusions: The rate of familial NPC in our study is 15.5%. Siblings are more commonly affected, and the interval between 2 affected siblings is relatively short. No distinct clinical pattern exists in familial NPC. We recommend that siblings of NPC patients be screened as soon as possible once the index case is diagnosed.

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fined as NPC occurring in 2 or more first-degree relatives within the same family. Hence, the patients in group 1 had at least 1 first-degree relative with NPC. First-degree relatives refer to parents, siblings, or children. The index NPC patient refers to the affected NPC patient in our study. The relationship between affected relatives and the time from the diagnosis of the affected relative to the diagnosis of the index NPC patient was noted. Because our study defined familial NPC as being limited to first-degree relations, patients with relatives such as uncles and cousins with NPC were included in group 2. The demographic data and clinical and pathological variables were recorded and compared between the 2 groups of patients. Staging was performed using the 1997 American Joint Committee on Cancer and International Union Against Cancer classification. Stage I and II disease was classified as early NPC, while stage III and IV disease was classified as advanced NPC. Statistical analysis of the variables between the 2 groups was performed.

RESULTS

Of the 200 patients with NPC, 35 (17.5%) had a relative with NPC; 31 were first-degree relatives, and 4 were second-degree relatives. The rate of familial NPC in this series was 15.5% (31 of 200 patients). All of these 31 patients with familial NPC had only a single affected first-degree relative. The 4 patients with second-degree relatives with NPC were included in group 2.

The relationship between the index NPC patients and their affected first-degree relatives is shown in Figure 1. Of the 31 patients with familial NPC, 9 (29%) of the affected first-degree relatives were parents (5 fathers and 4 mothers). In the remaining 22 (71%) of the familial NPC patients, the affected first-degree relatives were siblings. Of these siblings, 17 were brothers and 5 were sisters.

The mean (SD) interval between an affected first-degree relative and the index NPC patient was 12.1 (12.0) years (range, 5 months–43 years). The mean (SD) interval between an affected parent and the index NPC patient was 24.5 (12.1) years (range, 8–43 years). Between 2 affected siblings, the mean (SD) interval was 5.3 (5.3) years (range, 5 months–16 years).

The clinical variables of the patients with familial NPC were similar to those of the group with nonfamilial NPC.

COMMENT

Undifferentiated NPC is a common cancer in Singapore, and its incidence has remained largely stable during the past 10 years. The associated causative factors include infection with Epstein-Barr virus and an underlying genetic predisposition. This study clearly shows the existence of familial NPC, defined as NPC occurring in at least 1 family member. Further research is needed to elucidate the genetic factors that predispose to familial NPC.

Table. Clinical Factors for Patients With Familial and Nonfamilial NPC

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Familial NPC <em>(n = 31)</em></th>
<th>Nonfamilial NPC <em>(n = 169)</em></th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male-female ratio</td>
<td>5.2:1</td>
<td>2.8:1</td>
<td>.17</td>
</tr>
<tr>
<td>Age, y†</td>
<td>48.0 (9.2)</td>
<td>49.7 (12.6)</td>
<td>.46</td>
</tr>
<tr>
<td>Chinese race</td>
<td>93.5</td>
<td>91.7</td>
<td>.46</td>
</tr>
<tr>
<td>Symptom duration, mo†</td>
<td>2.3 (1.4)</td>
<td>3.4 (4.6)</td>
<td>.22</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck lumps</td>
<td>46.7</td>
<td>56.4</td>
<td>.51</td>
</tr>
<tr>
<td>Blood-stained sputum</td>
<td>43.3</td>
<td>34.8</td>
<td>.37</td>
</tr>
<tr>
<td>Unilateral deafness</td>
<td>23.3</td>
<td>29.2</td>
<td>.87</td>
</tr>
<tr>
<td>IgA/VCA level, &lt;=40</td>
<td>41.2</td>
<td>22.7</td>
<td>.13</td>
</tr>
<tr>
<td>IgA/EA level, &lt;=10</td>
<td>23.5</td>
<td>34.7</td>
<td>.57</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>12.9</td>
<td>11.8</td>
<td>.49</td>
</tr>
<tr>
<td>II</td>
<td>38.7</td>
<td>26.0</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>22.6</td>
<td>31.4</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>25.8</td>
<td>30.8</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EA, early antigen; NPC, nasopharyngeal carcinoma; VCA, viral capsid antigen.

*Data are given as percentage of each group unless otherwise indicated.
†Data are given as mean (SD).
Our study confirmed the findings in a recent study by no potential in using specific clinical or pathological fac-
in symptoms between the 2 groups. Therefore, there is
milial and nonfamilial NPC. There were no differences
between the 2 groups of patients did not reveal any sig-
possess distinct clinical characteristics. Our clinical data
do so with greater likelihood of having stage III or IV dis-
screened population of first-degree relatives of NPC pa-
stuates would support our view that this group forms an im-
portant target for screening. This study did not set out to
identify any correlation in genetic factors between the af-
fected relatives. Indeed, shared environmental risk fac-
tors may be just as important as genetic factors in the group
of patients we defined as having familial NPC. In our study,
familial NPC does not imply an exclusive genetic cause
or shared environmental risk factors. Our premise was that
we first had to determine if the rate of familial NPC was
high enough to warrant targeting first-degree relatives of
NPC patients for screening.

Our data also showed that the stage of disease be-
tween familial and nonfamilial NPC is similar. In an un-
screened population of NPC patients, most would have
stage III or IV disease. If, therefore, follows that in an un-
screened population of first-degree relatives of NPC pa-
tients, those who will eventually develop NPC will also
do so with greater likelihood of having stage III or IV dis-
ease. However, if these relatives were screened, the po-
tential will be that the disease may be diagnosed at an
earlier stage. This could have important consequences in
improving survival rates.

Although the entity of familial NPC exists, it does not
possess distinct clinical characteristics. Our clinical data
between the 2 groups of patients did not reveal any sig-
nificant differences. Sex, age, and race were similar in fa-
milial and nonfamilial NPC. There were no differences
in symptoms between the 2 groups. Therefore, there is
no potential in using specific clinical or pathological fac-
tors to differentiate between familial and nonfamilial NPC.
Our study confirmed the findings in a recent study by
Ung et al,12 which had indicated that familial NPC as a clini-
cal entity does not exist. It then follows that using clinical
or pathological variables is unlikely to help us
identify which first-degree relatives of index NPC pa-
tients will develop the disease. The implication of this
fact is that while first-degree relatives should be screened,
the optimal method of screening needs to be clarified.

There are certain characteristics in our series of pa-
tients with familial NPC that would help us plan a screen-
ing program. The affected first-degree relatives were most
commonly siblings of index NPC patients. Indeed, of the
31 affected relatives, only siblings and parents were in-
volved. The male preponderance in familial NPC is not
surprising, given the fact that NPC occurs more com-
monly in men. These characteristics of familial NPC al-
low further refinement of the target population for a
screening program. It is clear that only siblings and chil-
dren of affected NPC patients need to be screened, be-
cause it is unlikely that the parents of an affected NPC
patient will develop the disease. The mean interval be-
tween affected siblings is 5.3 years (range, 5 months–16
years), while that between an affected parent and a child
is 24.5 years (range, 8–43 years). Data from the Sin-
gapore Cancer Registry show that the incidence of NPC
in men starts to increase from the age group of 25 to 30
years at 2.5 per 100 000 and peaks at the age group of 45
to 50 years at 55.7 per 100 000. It remains high even at
the age group of older than 80 years, with the incidence
rate being 19.7 per 100 000. The information from our
study and from the Singapore Cancer Registry provides
evidence-based planning for the age group at which first-
degree relatives of NPC patients should be screened. Once
an NPC patient is diagnosed as having the disease, we
recommend that all the siblings should be screened. Based
on our data, the longest duration between 2 affected sib-
lings was 16 years. The inference would be that if a sib-
ling of an NPC patient was screened for at least 16 years
without developing the disease, this sibling's chances of
being diagnosed as having NPC will be low. Therefore,
the evidence would suggest a reasonable screening pe-
riod of 20 years for all siblings. Beyond 20 years, sib-
lings who had been screened and did not develop NPC
are not likely to be diagnosed as having the disease. While
we recommend that children of NPC patients be screened,
the exact age of the children to be screened is debatable.
We suggest that children should be screened from the
age of 25 years. The rationale for such a recommenda-
tion is based on the fact that the mean interval between
affected parent and child in our series was 24 years, and
that the incidence in our population only increases sig-
nificantly from the age of 25 years. While it is clear that
siblings are a reasonable high-risk target group for screen-
ing NPC, the ability to diagnose these siblings at an early
stage of disease remains to be proved. Toward this end,
we have embarked on a prospective program to screen
the siblings of all our patients newly diagnosed as hav-
ing NPC. In addition to a detailed medical history, the
siblings will have an examination of the nasopharynx.
Measurements of IgA/viral capsid antigen and IgA/early
antigen and plasma Epstein-Barr virus DNA will be per-
formed. We will assess the role of plasma Epstein-Barr
virus DNA in detecting early NPC. In the coming years,
we will expect to have an answer with regard to the ef-
cacy of such a screening program. Our present study
supports the feasibility of screening first-degree rela-
tives of NPC patients. However, as in any screening pro-
gram, many challenges need to be overcome, not the least
of which is to be able to ensure that all the targeted popu-
lation is reached. This screening program can only be con-
sidered a success if the survival rates are improved.

In conclusion, the rate of familial NPC in our study
is 15.5%. While all first-degree relatives should be
screened for NPC, siblings of the index NPC patients
should be screened as soon as possible. A prospective
program is necessary to determine the efficacy of screening siblings.

Submitted for Publication: May 10, 2005; final revision received July 16, 2005; accepted August 22, 2005. Correspondence: Kwok Seng Loh, FRCS, Department of Otolaryngology–Head & Neck Surgery, National University Hospital, 5 Lower Kent Ridge Rd, Singapore 119074 (entv5@nus.edu.sg). Financial Disclosure: None. Previous Presentation: This study was presented at the Sixth International Conference on Head and Neck Cancer; August 10, 2004; Washington, DC.

REFERENCES


Announcement

New Address for Editorial Office

The ARCHIVES editorial office has moved. Effective October 1, 2005, the editorial office address is as follows: Paul A. Levine, MD, Archives of Otolaryngology–Head and Neck Surgery, 183 Tuckahoe Farm Ln, Charlottesville, VA 22901; telephone, 434-960-9202 or 434-960-9203; fax, 434-973-3454. Manuscripts should continue to be submitted electronically through ejournalPress via the journal Web site (http://manuscripts.archoto.com).