Prevalence of Idiopathic Hypoparathyroidism and Pseudohypoparathyroidism in Japan

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A nationwide epidemiologic survey of idiopathic hypoparathyroidism and pseudohypoparathyroidism was conducted in 1998 to clarify the prevalence of the two disorders in Japan. From a total of 14,100 departments of pediatrics, internal medicine, neurology, and endocrinology in whole Japan, 2952 (20.9%) study departments were selected at random. Of these departments receiving the first questionnaire, 1855 (62.8%) responded. From these departments 390 patients with idiopathic hypoparathyroidism and 203 with pseudohypoparathyroidism who visited the hospitals in 1997 were reported. The total numbers of patients were estimated to be 900 (690-1100) for idiopathic hypoparathyroidism and 430 (330-520) for pseudohypoparathyroidism (95% confidence intervals in parentheses). Using these data, the period prevalence of the diseases were 7.2 (5.5-8.8) per million population in idiopathic hypoparathyroidism, and 3.4 (2.6-4.2) in pseudohypoparathyroidism (95% confidence intervals in parentheses). J Epidemiol, 2000; 10: 29-33

Hypoparathyroidism is a rare disease and its epidemiologic features are still unclear. For example, leading textbooks of internal medicine 1,2 do not describe frequency of the disease. In Japan, the Research Committee conducted a nationwide survey, and the number of patients with pseudohypoparathyroidism was 69 between 1967 and 1976. 3 In Israel, the number of patients with idiopathic hypoparathyroidism was 24 (23 Jewish persons and one non-Jewish) between 1972 and 1978. 4 Unfortunately, we could not find out epidemiologic papers about hypoparathyroidism other than these articles. This fact may reflect the characteristics of the disease, a rare disease.

In 1998, the Research Committee on Epidemiology of Intractable Disease (Chairman: Yoshiyuki Ono), and the Hormone Receptor Abnormality Research Committee (Chairman: Masato Kasuga), sponsored by the Ministry of Health and Welfare of the Japanese government, conducted jointly a nationwide survey of hypoparathyroidism in Japan, and this article reports the prevalence of the diseases.

MATERIALS AND METHODS

A nationwide mail survey for hypoparathyroidism was conducted in 1998 in Japan. The target patients were those who visited hospitals because of the disease in 1997. According to the Nationwide Epidemiologic Survey Manual issued by the Research Committee on Epidemiology of Intractable Disease,

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we selected 3 departments for the survey target: departments of pediatrics, internal medicine, and neurology. Study hospitals were selected randomly from a list with all hospitals in Japan. The selection rate was decided according to the stratification classified by the number of bed in the hospital; the more beds a hospital has, the higher the probability to be selected was. The selection rate was 100% for hospitals with more than or equal to 500 beds and university hospitals, whereas only 5% of hospitals with less than 100 beds were selected at random. Besides the 3 departments, we designated a department of endocrinology as a special department, and all of the special departments in Japan were selected as the study department. After the selection of the study departments, we sent a questionnaire with diagnostic guidelines (see appendix). The first survey asked only the numbers of patients with idiopathic hypoparathyroidism and pseudohypoparathyroidism that visited the hospital in 1997. If a department responded that there was (were) a patient(s), the second mail survey questionnaire asking detail clinical features for each patient was sent. We discuss only the prevalence in the current study.

Considering the selection rate and the response rate to the survey, we estimated the total numbers of patients with idiopathic hypoparathyroidism and pseudohypoparathyroidism. The formula for estimation is:

\[
\text{The estimated total number of patients} = \frac{\text{reported number of patients}}{\text{selection rate} \times \text{response rate}} = \frac{\text{reported number of patients}}{\frac{\text{number of reporting departments}}{\text{number of total departments}}}.
\]

Ninety-five percent confidence intervals were calculated with an assumption of multinomial hypergeometric distribution. Age and sex distributions of the 2 conditions were observed according the patients that were reported to the second survey.

### RESULTS

From a total of 14,100 departments of pediatrics, internal medicine, neurology, and endocrinology in whole Japan, 2952 (20.9%) study departments were selected at random. Of these departments receiving the first questionnaire, 1855 (62.8%) responded. From these departments 390 patients with idiopathic hypoparathyroidism and 203 with pseudohypoparathyroidism were reported. The numbers of patients by sex, disease and department were shown in Table 1. Although almost the same numbers for male and female patients were reported as idiopathic hypoparathyroidism, male/female ratio of pseudohypoparathyroidism was rather small (0.74). The total numbers of patients were estimated to be 900 (690-1100) for idiopathic hypoparathyroidism and 430 (330-520) for pseudohypoparathyroidism (95% confidence intervals in parentheses). Using these data, the period prevalence of the diseases were 7.2 (5.5-8.8) per million population in idiopathic hypoparathyroidism, and 3.4 (2.6-4.2) in pseudohypoparathyroidism (95% confidence intervals in parentheses).

The numbers of patients by disease, age class, and sex who were reported to the second survey are shown in Table 2. The age and sex distributions of 197 patients with idiopathic hypoparathyroidism and 117 patients with pseudohypoparathyroidism are revealed. Relative frequency of age distribution by disease and sex are shown in parentheses. In comparison with idiopathic hypoparathyroidism, the age distribution of pseudohypoparathyroidism is skewed to the left (young generation). In idiopathic hypoparathyroidism, females were distributed almost equally from young generation to the old, whereas the number of males aged 20-29 years was relatively small and the number of males aged 40-59 was large.

### DISCUSSION

Epidemiologic studies about hypoparathyroidism has been few in the world. Therefore, two of the major textbooks in internal medicine do not mention the epidemiologic features, such as the number of patients, incidence rate, and prevalence.
Hypoparathyroidism in Japan

Table 2. Age distribution, by disease and sex.

<table>
<thead>
<tr>
<th>Age(year)</th>
<th>Idiopathic hypoparathyroidism</th>
<th>Pseudohypoparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>0-9</td>
<td>9(8)</td>
<td>7(9)</td>
</tr>
<tr>
<td>10-19</td>
<td>16(14)</td>
<td>12(15)</td>
</tr>
<tr>
<td>20-29</td>
<td>6(5)</td>
<td>13(16)</td>
</tr>
<tr>
<td>30-39</td>
<td>14(12)</td>
<td>14(17)</td>
</tr>
<tr>
<td>40-49</td>
<td>23(21)</td>
<td>13(16)</td>
</tr>
<tr>
<td>50-59</td>
<td>26(23)</td>
<td>11(13)</td>
</tr>
<tr>
<td>60-69</td>
<td>12(11)</td>
<td>8(10)</td>
</tr>
<tr>
<td>70-79</td>
<td>5(4)</td>
<td>3(4)</td>
</tr>
<tr>
<td>80+</td>
<td>1(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>Total</td>
<td>112(100)</td>
<td>82(100)</td>
</tr>
</tbody>
</table>

Total is not sum of each sex because sex unknown is included.
Percentages in parentheses. The total does not sum 100% because of the rounding.

The reason of the rare epidemiologic studies may be because it is very rare disease. This is the study following that in 1967-1976 for pseudohypoparathyroidism in Japan, and the first one for idiopathic hypoparathyroidism.

Several physical disorders induce hypoparathyroidism, and this study focuses the two idiopathic conditions excluding other secondary physical disorders that induce hypoparathyroidism, such as post-surgical operation. The idiopathic conditions are classified into two by the levels of serum parathyroid hormone, idiopathic hypoparathyroidism with a low level of parathyroid hormone, and pseudohypoparathyroidism with a high level. The Hormone Receptor Abnormality Research Committee targets only the second one because pseudohypoparathyroidism is a receptor dysfunction of parathyroid hormone. However, in the diagnostic guidelines (see appendix), there is only one difference between the two conditions; the serum hormone levels. Therefore, we selected the two diseases as a target of the current study.

The only study that have shown the incidence rate of idiopathic hypoparathyroidism is from Israel. This paper reported that 23 Jewish new patients with idiopathic hypoparathyroidism were observed between 1972 and 1978. At that time the Jewish population in Israel was 2.7 million; the annual incidence rate for Jewish people was, therefore, 1.2/million population. In addition, the authors of the Israel paper had had an impression that the disease was more prevalent among Jewish people, and their data indicated that this was true, in particular among Iranian Jewish. The current data in Japan are period prevalence and cannot be comparable to the Israel data directly. In consideration with the long duration of the disease, however, the frequency of idiopathic hypoparathyroidism may be lower in Japan than among Jewish people. For example, our current data shows that the period prevalence of idiopathic hypoparathyroidism was 7.2 per million population, and the annual incidence rate should be 0.72 per million if the average duration of the disease is 10 years.

The number of patients with pseudohypoparathyroidism in the previous study was not directly comparable with the current results because the previous one was period prevalence during 10 years and the current one is that during 1 year. However, the observed number of patients with pseudohypoparathyroidism seemed to increase during the recent 20 years. When the increasing frequency of a disease is observed, we have to certify whether the true incidence or prevalence increases or not. If the recognition or diagnostic procedures changes, we can observe the increase without the true change. The symptoms and laboratory findings of pseudohypoparathyroidism are so specific that recognition may not relate the increase. Besides, the disease is congenital, and some adult patients existed; therefore we may conclude that the prolonged duration of illness in individual patients due to the progression of treatment increased period prevalence.

Because we used a random sampling method in this study, validity of the estimated number of patients is a great issue. Besides, the response rate was not 100%, which should induce bias. Several mathematical methods have been proposed to treat the non-response facilities in surveys like this, but the simple method by which the estimated number is the number of reported patients divided by the response rate is the best if we have no other information about non-response facilities. In addition, the estimated number of patients with idiopathic thrombocytopenic purpura using this method was 1.1 times as large as the real number of patients; the bias induced by the method did not seem so serious. Age and sex distribution of the disorders shown in Table 2 is based on the secondary survey, in which some departments that responded the first survey did not answered. This also induces another bias, but we can use the same theory as mentioned above and the age and sex distribution is reflects the true epidemiologic features of the disorders in spite of the response rate.
Appendix. Diagnostic guidelines of idiopathic hypoparathyroidism and pseudoparathyroidism for the nationwide epidemiologic survey, by the Hormone Receptor Abnormality Research Committee, Ministry of Health and Welfare.

1. Idiopathic hypoparathyroidism
   a. Low level of serum intact parathyroid hormone
      Serum intact parathyroid hormone < 30 pg/ml
   b. Hypocercemia
      Serum calcium < 8.5 mg/dl
   c. Absence of decreased serum phosphate (increase or normal)
      Serum phosphate equal to or greater than 3.5 mg/dl (15 years of age or older)
      Serum phosphate equal to or greater than 4.5 mg/dl (<15 years of age)
   d. Absence of renal dysfunction
      Serum BUN equal to or less than 30 mg/dl
      or serum creatinine equal to or less than 2 mg/dl
   e. Not to be the results of other diseases (e.g. hyperthyroidism), nor secondary symptoms of other diseases

2. Pseudopyparathyroidism
   a. High level of serum intact parathyroid hormone
      Serum intact parathyroid hormone equal to or greater than 30 pg/ml
   b. Hypocercemia
      Serum calcium < 8.5 mg/dl
   c. Absence of decreased serum phosphate (increase or normal)
      Serum phosphate equal to or greater than 3.5 mg/dl (15 years of age or older)
      Serum phosphate equal to or greater than 4.5 mg/dl (<15 years of age)
   d. Absence of renal dysfunction
      Serum BUN equal to or less than 30 mg/dl
      or serum creatinine equal to or less than 2 mg/dl
   e. Not to be the secondary symptoms of other diseases, such as renal tubular dysfunction

References


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