ORIGINAL CONTRIBUTION

A Case-control Study of Ossification of the Posterior Longitudinal Ligament of the Spine in Japan

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To determine whether several factors affect the occurrence of ossification of the posterior longitudinal ligament of the spine (OPLL), we conducted a case-control study in Japan in 1988-90. Patients selected for the study were receiving financial aid for treatment of the disease; the equal number of population-based controls matched by age and sex were selected. Age-adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated using conditional logistic regression models. A medical history of hypertension increased the risk of OPLL (OR=1.58; 95% CI, 1.01-2.46), and so did injury with hospitalization (OR=1.83; 95% CI, 1.14-2.93) and blood transfusion (OR=1.77; 95% CI, 1.01-3.10). On the other hand, indoor working (OR=0.65; 95% CI, 0.44-0.96) and a medical history of allergic rhinitis (OR=0.35; 95% CI, 0.15-0.84) decreased the risk. After adjustment for these factors each other, similar trends still existed. J Epidemiol, 1995; 5: 29-33.

Ossification of the posterior longitudinal ligament of the spine (OPLL) causes myelopathy by compressing the spinal nerve with ossified ligaments. After the first report of the disease from Japan in the world, it has been more prevalent in Japan than in other countries1-6). Although some factors such as genetic ones7-9) and a medical history of diabetes mellitus8) have been pointed out as risk factors of the disease, no case-control study has explored the risk factors to the best of our knowledge. Therefore, even whether such basic factors as smoking and alcohol consumption elevate the risk of OPLL is still unclear.

To clarify whether basic risk factors of other diseases, such as smoking, alcohol consumption, occupation, and medical histories, increase or decrease the risk of OPLL, the Epidemiology of Intractable Diseases Research Committee conducted a case-control study of the disease.

MATERIALS AND METHODS

Between 1988 and 1990, the Epidemiology of Intractable Diseases Research Committee, Ministry of Health and Welfare of the Japanese Government performed a case-control study of OPLL by comparing 239 patients who were receiving financial aid for treatment of the disease with a group of 239 controls matched to the study group by age, sex, and place of residence. Of approximately 850...
public health centers in Japan, 93 centers were selected to collect data for this study.

**Patients**

Patients selected for the study were residents of the areas covered by the aforementioned 93 participating public health centers. All had been diagnosed with OPLL, and all had begun to receive financial aid for treatment of the disease between April 1988 and March 1990.

In Japan, there is a public medical aid system for 35 “intractable” diseases as of January 1994, one of which is OPLL. A patient with OPLL who needs financial aid to obtain treatment applies for aid through a public health center that takes charge of the municipality wherein the patient resides. To apply for the aid, the patient must submit a complete application form with a certificate issued by a physician that supports the diagnosis and includes radiographic findings of the spine. Each of the 47 prefectural governments in Japan has a special committee comprised of medical specialists who treat specific diseases. The committee examines the certificate submitted by an applicant and determines whether the diagnosis is correct. The committee’s examination usually depends on the clinical features of the disease and the radiographic findings. A patient’s eligibility for the financial aid is dependent on the committee’s opinion and is not based on the patient’s family income. After acceptance for the aid by the committee, the public health center gives the patient a booklet as certification for the eligibility of treatment with the aid. Thus, the patients in this study were diagnosed as having OPLL by their physicians, and in each case, diagnoses were recognized as correct by the prefectural committees.

Between April 1988 and March 1990, officers in charge of the financial aid programs in the 93 participating public health centers asked all patients with OPLL who had been recently accepted into the program to participate in the study when they came to the centers to obtain the booklets. The officers described the purpose of the study and how data would be obtained. Those who agreed to participate were considered eligible for the study. A total of 239 eligible cases were identified.

**Controls**

Healthy subjects matched to the study group by age and sex were selected as controls. When officers in each of the 93 public health centers recruited a case for the study, they then randomly selected a potential control of the same sex and age range (within 5 years) from the roster of a health check-up program in the center. Public health centers have health check-up programs open to all residents without or with little examination fees. Each control was selected from the public health center that took care of the corresponding case; place of residence for cases and controls was therefore similar as well. The potential control subjects who agreed to participate in the study and received explanation of the purpose and the data collection methods were considered eligible for the study. A total of 239 eligible controls were identified.

**Data Collection**

We developed a self-administered questionnaire for data collection that requested the following information: name, address, sex, date of birth, date of disease onset, smoking habits, level of alcohol consumption, occupation, family history, and medical history. Cases were requested to answer the questionnaire according to their condition before onset of the disease. The dates of disease onset were certified by the diagnostic certificates submitted at the time of application for the aid. The details of obtained information are shown in Table 2.

Each of the eligible cases and controls received a questionnaire and a stamped envelope in the public health center. Officers had written in the person’s name, address, sex, and date of birth. Participants filled out the questionnaires at home and returned them to the public health center by mail. When questionnaires were received by the public health center, officers checked them to make certain all questions had been answered. The officers tried to obtain information by phone from subjects who failed to answer some of the questions.

To analyze the data, we gathered all questionnaires checked by officers in the public health centers. Name and address were detached from the questionnaires, thus blinding investigators to the identities of the subjects.

We determined the smoking habits of each participant by using information such as the date of smoking cessation and the date of disease onset. We classified a case who had stopped smoking after onset as a current smoker even though he or she might not have been a smoker at the time of the survey.

| Table 1. Sex and age distribution of the 239 cases with ossification of the posterior longitudinal ligament and 239 controls, Japan, 1988-90. |
|---|---|---|
| Characteristics | Case | Control |
| Sex | | |
| male | 156 (65.3) | 156 (65.3) |
| female | 83 (34.7) | 83 (34.7) |
| Age (year) | | |
| <39 | 9 (3.8) | 9 (3.8) |
| 40-49 | 49 (20.5) | 53 (22.2) |
| 50-59 | 90 (37.7) | 90 (37.7) |
| 60-69 | 85 (35.6) | 79 (33.1) |
| 70+ | 6 (2.5) | 8 (3.3) |
Table 2. Crude odds ratios\(^a\) (ORs) and 95% confidence intervals (CIs) for ossification of the posterior longitudinal ligament to observed exposures before the onset, Japan, 1988-90.

| Exposure (referent group) | Proportion of exposure (%) | OR (95% CI) |
|--------------------------|-----------------------------|-------------|
|                          | case | control | |
| Smoking habit             |      |         | |
| current smoker (non-smoker) | 38.5 | 36.0 | 1.31 (0.77-2.23) |
| ex-smoker (non-smoker)    | 18.8 | 18.4 | 1.18 (0.63-2.21) |
| Alcohol-drinking habit     |      |         | |
| ≥1 day per week (<1 day per week) | 40.6 | 46.0 | 0.70 (0.46-1.07) |
| Occupation                |      |         | |
| white-collar worker (blue-collar worker) | 28.7 | 34.3 | 0.67 (0.44-1.01) |
| sedentary work (standing work) | 22.2 | 22.2 | 0.92 (0.60-1.42) |
| shift work (no)           | 20.4 | 15.3 | 1.43 (0.87-2.35) |
| indoor work (outdoor work) | 47.7 | 54.6 | 0.65 (0.44-0.96) |
| dusty condition (no)      | 33.3 | 24.5 | 1.44 (0.96-2.15) |
| noisy condition (no)      | 33.8 | 24.5 | 1.47 (0.98-2.21) |
| difficulties in human relations (no) | 27.8 | 21.3 | 1.31 (0.86-1.99) |
| Dinner style in childhood  |      |         | |
| sitting on a tatami mat (using a table and a chair) | 93.3 | 93.7 | 0.81 (0.36-1.82) |
| Medical history before the onset |      |         | |
| apoplexy (no)             | 0.4  | 0.8   | 0.42 (0.04-4.69) |
| hypertension (no)         | 25.1 | 16.7  | 1.58 (1.01-2.46) |
| diabetes mellitus (no)    | 10.0 | 7.1   | 1.46 (0.75-2.84) |
| rheumatoid arthritis (no) | 2.1  | 1.3   | 1.73 (0.41-7.32) |
| bronchial asthma (no)     | 2.9  | 1.7   | 1.47 (0.42-5.14) |
| allergic rhinitis (no)    | 3.3  | 8.4   | 0.35 (0.15-0.84) |
| injury with hospitalization (no) | 24.3 | 15.1 | 1.83 (1.14-2.93) |
| surgical operation (no)   | 52.3 | 48.5  | 1.19 (0.82-1.72) |
| blood transfusion (no)    | 16.7 | 10.9  | 1.77 (1.01-3.10) |
| Medical history of family members\(^b\) |      |         | |
| hypertension (no)         | 37.2 | 32.6  | 1.30 (0.87-1.93) |
| malignant neoplasms (no)  | 29.3 | 26.4  | 1.15 (0.76-1.75) |
| diabetes mellitus (no)    | 15.1 | 10.9  | 1.42 (0.81-2.50) |
| rheumatoid arthritis (no) | 7.1  | 4.6   | 1.37 (0.61-3.08) |
| OPLL\(^c\) (no)           | 4.2  | 0.0   | —              |
| Consanguinity marriage\(^d\) (no) | 5.9  | 6.3   | 0.87 (0.41-1.87) |

\(^a\): Adjusted only for age.
\(^b\): Including only parents, brother(s), sister(s), and child(ren).
\(^c\): Ossification of the posterior longitudinal ligament.
\(^d\): Including only a marriage between cousins among parents or grandparents.

**Data Analysis**

We evaluated the association between a factor determined in the questionnaire and OPLL by calculating an odds ratio (OR) with 95% confidence interval (CI) using the conditional logistic models\(^{10}\). First, a crude OR for each of the factors, which was adjusted for only age, was estimated. Second, factors with statistically significant ORs in the crude analyses, of which 95% CIs did not include unity, were involved in a model simultaneously as a multivariable conditional logistic analysis to explore whether some of them were confounding factors. The program used was PROC PHREG of the SAS Institute\(^{11}\).

**RESULTS**

Age and sex distributions of the 239 cases with OPLL and 239 controls are shown in Table 1. The mean age of cases was 56.1 years (+8.8 years SD) and that of controls was 55.5 (+8.7 years SD). Thus, there was no difference in age distribution between cases and controls.

Out of 26 factors observed, which are shown in Table 2, 5 had statistically significant ORs, of which 95% CIs did not include the unity; indoor work (vs. outdoor work), history of hypertension (vs. no), history of allergic rhinitis
Some clinical observations suggest the possibility of incessantly inflicted stresses on the posterior longitudinal ligament inducing the development of OPLL. If an injury changes the align of the vertebrae with or without clinical symptoms, this may be a stress. High blood pressure may also be a stress. On the other hand, heterotropic ossification is related to injuries as well. Thus, injuries, unfortunately not specified in this study, may stimulate the posterior longitudinal ligament, and this stimulation may be a trigger of the ossification.

Recent studies have suggested relationship between OPLL and immunologic and hormonal factors. Although we cannot indicate any hypotheses, the fact that the histories of allergic rhinitis and blood transfusion would be able to be explained as the risk factors of OPLL.

Although the OR could not be estimated because no control had the factor, we should pay attention to the fact that 10 out of 239 cases or 4.2% had a medical history of apoplexy and allergic rhinitis were less than 0.5. In other words, all of the ORs except these two were between 0.5 and 2.0.

To exclude effects as a confounding factor for each other, these 5 significant factors were included in the logistic model at the same time, and ORs were estimated. As shown in Table 3, all of the 5 ORs were similar to those in the crude analyses, although none of the factors showed statistical significance.

Univariable analyses by sex were also done and similar trends with wider 95% CIs than shown in Table 2 were observed.

**DISCUSSION**

This is the only case-control study of OPLL with a large sample size; because this disease is not so prevalent in other countries as in Japan, a case-control study with such a large sample size may impossible outside Japan. Besides, even though it is more prevalent in Japan, the incidence rate and prevalence are so low that a hospital-based case-control study of OPLL seems impossible. Of the observed 26 potential risk factors, the medical histories of hypertension, injury with hospitalization and blood transfusion increased the risk of OPLL, and the indoor working and the history of allergic rhinitis decreased the risk significantly. The trends still existed after the adjustment of one another.

In spite of the statistical significance of the 5 factors, the ORs were not so far from unity: 0.65 for the indoor working, 1.58 for the history of hypertension, 0.35 for the history of allergic rhinitis, 1.83 for the history of injury with hospitalization, and 1.77 for the history of blood transfusion. Therefore, none of the factors we observed could contribute to the prevention of the disease. However, the facts may give us some hints for the etiology of OPLL.

Some clinical observations suggest the possibility of

| Table 3. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for ossification of the posterior longitudinal ligament to the five statistically significant exposures in the crude analyses (table 2), Japan, 1988-90. |
| Exposure (referent group) | OR (95% CI) |
|---------------------------|-------------|
| Indoor work (outdoor work) | 0.70 (0.46-1.04) |
| Medical history before the onset hypertension (no) | 1.55 (0.98-2.45) |
| allergic rhinitis (no) | 0.42 (0.17-1.02) |
| injury with hospitalization (no) | 1.60 (0.98-2.62) |
| blood transfusion (no) | 1.47 (0.81-2.65) |

(vs. no), history of injury with hospitalization (vs. no), and history of blood transfusion (vs. no). No OR was over 2.0, whereas ORs for medical history of apoplexy and allergic rhinitis were less than 0.5. In other words, all of the ORs except these two were between 0.5 and 2.0.

To exclude effects as a confounding factor for each other, these 5 significant factors were included in the logistic model at the same time, and ORs were estimated. As shown in Table 3, all of the 5 ORs were similar to those in the crude analyses, although none of the factors showed statistical significance.

Univariable analyses by sex were also done and similar trends with wider 95% CIs than shown in Table 2 were observed.
Epidemiology of Intractable Diseases Research Committee has conducted case-control studies for some other diseases using same selection methods\(^{1,10}\), and the advantages and disadvantages of the methodologic issue has already been discussed\(^{18,19}\). In spite of the disadvantages, our control selection methods have satisfied three principles proposed by Wacholder, et al.\(^{20}\); principles of study base, deconfounding, and comparable accuracy. In terms of OPLL, the number of subjects aged 70+ years is relatively small according to the age distribution of the disease in Japan\(^{6}\). This is due to the small numbers of application to the aid system of this age class persons for not only OPLL but also other diseases because of the medical insurance system by Health for the Elderly Act of 1982\(^{21}\).

Finally, all eligible patients were asked to participate in the study when they were recognized to be eligible for aid. Therefore, it seems possible that perhaps 80% of them were incident cases.

In conclusion, the current case-control study indicate some risk factors of OPLL such as indoor working, medical histories of hypertension, allergic rhinitis, injuries with hospitalization, and blood transfusion. However, all of the ORs observed, including even those with statistical significance, were not so far from 1.0. Although the OR was not so high but was significant, injuries are suspected to be a trigger of the disease.

**Acknowledgment**

The authors thank the staff of public health centers and the prefectural governments that participated in this study for assistance with data collection.

This work was supported by the Epidemiology of Intractable Diseases Research Committee, the Ministry of Health and Welfare the Japanese Government (former chairperson: Dr. Hiroshi Yanagawa) as a research project.

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