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A nationwide epidemiological survey of alpha$_1$-antitrypsin deficiency in Japan

Kuniaki Seyama[a,*], *Toyohiro Hirai*[b], *Michiaki Mishima*[b], *Koichiro Tatsumi*[c], *Masaharu Nishimura*[d], *The Respiratory Failure Research Group of the Japanese Ministry of Health, Labour, and Welfare*

[a]*Division of Respiratory Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-Ku, Tokyo 113-8421, Japan*
[b]*Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan*
[c]*Department of Respirology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8677, Japan*
[d]*First Department of Medicine, Hokkaido University School of Medicine, 14-5, Kita-Ku Kita, Sapporo 060-8648, Japan*

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ABSTRACT

Background: Alpha$_1$-antitrypsin (AAT) deficiency (AATD), a condition of little or no AAT in the serum, is believed to be extremely rare in Japan. However, no such nationwide epidemiological survey has been conducted. The Respiratory Research Failure Group and Japanese Respiratory Society (JRS) cooperated to conduct this survey.

Methods: The survey questionnaire was sent by post to 1598 hospitals that have 200 or more beds (excluding mental hospitals), and by e-mail to members of the JRS. Hospitals failing to respond were followed-up by phone.

Results: 1467 hospitals replied [response rate=91.8% (1467/1598)], and 114 members responded. Of the 14 probands registered from 10 hospitals and one local practitioner, 9 had severe and 5 had mild AATD. Eleven of these patients were diagnosed with COPD, 1 with COPD and bronchiectasis, 1 with pulmonary emphysema without airflow obstruction, and the remaining 1 with bronchiectasis without airflow obstruction. Mutation analysis of the *SERPINA1* gene was performed in 7 patients, 6 of whom (85.7%) had homozygous PI*S$_{iiyama}$. The prevalence of AATD in Japan was thus estimated to be 24 patients, with a 95% confidence interval (22, 27). When asked if they would prescribe AAT augmentation therapy, 6 of the 10 (60.0%) of respondent attending physicians answered affirmatively if health insurance would cover the treatment.

Conclusions: This nationwide survey confirmed that AATD is extremely rare in Japan. Six of 10 care-giving physicians would offer AAT augmentation therapy if the therapy were covered by health insurance in Japan.

Abbreviations: AAT, alpha$_1$-antitrypsin; AATD, alpha$_1$-antitrypsin deficiency; COPD, chronic obstructive pulmonary disease

*Corresponding author. Tel.: +81 3 5802 1063; fax: +81 3 5802 1617.
E-mail addresses: kseyama@juntendo.ac.jp (K. Seyama), t_hirai@kuhp.kyoto-u.ac.jp (T. Hirai), mishima@kuhp.kyoto-u.ac.jp (M. Mishima), tatsumi@faculty.chiba-u.jp (K. Tatsumi), ma-nishi@med.hokudai.ac.jp (M. Nishimura).

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1. Introduction

Alpha$_1$-antitrypsin (AAT) deficiency (AATD) is an autosomal recessive condition whose victims have an inborn absence or shrinkage of AAT (also called α_1-proteinase inhibitor) in their serum caused by mutations in the *SERPINA1* gene (a member of the SERPIN, serine protease inhibitor gene family), which is located on chromosome 14q32.1 [1]. Individuals with AATD bear a high risk of developing pulmonary emphysema and/or liver cirrhosis. Compared to those with normal AAT levels, patients with AATD usually acquire severe pulmonary emphysema at a young age and, when they progress to severe AATD, manifest chronic obstructive pulmonary disease (COPD) [1].

AATD was first described by Laurell and Eriksson in 1963 [2]. They described five patients with AATD evident by electrophoretic assay of serum protein; subsequently, an association between that condition and pulmonary emphysema became evident. Among Caucasians in the United States and European countries, the prevalence of AATD is high and estimated to be approximately one in 3000–6000 individuals. One to 2 percent of COPD patients are estimated to have AATD [1]. In North America and Europe, augmentation therapy with intravenous AAT is currently licensed for patients with AATD to increase serum AAT levels and to protect the lungs from the further progression of pulmonary emphysema. This protocol is the result of many studies documenting the efficacy of AAT augmentation therapy and of pooled analyses combining two recent double-blind clinical trials. The latter study confirmed that the progression of pulmonary emphysema was efficiently suppressed with AATD augmentation therapy when PD15 (15th percentile of lung density) was used as an index [3].

In contrast, AATD is extremely rare in Japan. In 2000, only 18 families were reported to have an abnormal *SERPINA1* gene (including one family having member(s) with abnormality of chromosome 14, and 2 families having a heterozygous carrier of the mutated *SERPINA1* gene) [4]. Among those 18 families, 15 had confirmed AATD [4]. The most frequent mutation causing severe AATD is called *PI*Z* among Caucasians, whereas *PI*S*$_{iiyama}$ was commonly found in the Japanese group, and none of them were positive for *PI*Z* [4]. However, neither the prevalence of AATD nor the actual number of AATD patients in Japan has been established, since no nationwide survey for AATD has ever been conducted in this country. Without this specific epidemiologic data, the necessity for augmentation therapy by administering intravenous AAT could not be properly evaluated. Therefore, this study was initiated to compile the current number of patients with AATD in Japan, to evaluate the need for AAT therapy, and to question physicians' opinions regarding their participation.

2. Patients and methods

We defined AATD as a serum AAT level less than 90 mg/dL (by nephelometry method), then sub-classified severe AATD [serum AAT <11 μM (50 mg/dL)] and mild AATD (serum AAT 50–90 mg/dL) [5]. A survey questionnaire prepared for recipients included the following inquiries: (1) the total number of patients diagnosed as having AATD in your hospital, (2) gender and age with month and year of birth of each AATD patient, (3) patient's consanguineous marriage noted or not, (4) the number of each patient's family members with AATD, (5) condition(s) or disease(s) currently caused by AATD, (6) each patient's symptoms, including severity of breathlessness (modified Medical Research Council grade [6]), (7) results of the patient's pulmonary function test, (8) patient's serum AAT level (by the nephelometry method), (9) causative mutations of the patient's *SERPINA1* gene, and (10) each patient's current medical treatment. We sent the survey questionnaires by postal mail to 1598 hospitals with 200 beds or more but excluded mental hospitals and children's hospitals, and by e-mail to about 9450 members of the Japanese Respiratory Society (JRS), i.e., about 75–80% of the entire JRS membership (Fig. 1). A cover letter was enclosed (or attached) asking each recipient to participate in this nationwide survey by filling out and returning the questionnaire. If no reply was forthcoming, we called the hospitals directly to see if they were willing to participate. This epidemiological study was approved by the Institutional Review Board of Juntendo University Hospital (IRB No. 2014010, August 2013); because of the anonymous nature of the data, the requirement for patient informed consent was waived.

3. Results

3.1. *The prevalence of AATD in Japan*

A flowchart of epidemiological survey is summarized in Fig. 1. E-mail surveys of JRS members yielded responses from 114 members, and four members registered patients with AATD. As for postal mail surveys, 659 of 1598 hospitals solicited responded by returning the completed survey questionnaires [response rate=41.2%]. To increase participation in the survey, we next focused on postal access, resent the survey questionnaires to the 939 hospitals that had not responded, awaited their response to the second mailing, and finally contacted the remaining non-responders by phone to ask for their co-operation. Finally, we obtained responses from 1467 hospitals [response rate=91.8% (1467/1598)] by postal survey.

Our survey identified 14 separate families with AATD from 10 hospitals and one local practitioner (Table 1). Patients 2 and 3 were registered from a single facility, and patients 9, 10, and 11 came from another facility at a different site. Fourteen probands with AATD and 8 other patients with AATD in total were documented. Of the 14 probands, nine patients had severe AATD whereas 5 were considered to be mild cases. Eight of these patients were male and six were female. The mean age of the probands at registration was 62.6 years old. Consanguineous marriage was reported in 3 families, marriage specified as non-consanguineous in 3 families, and unknown (not answered) in the remaining 8 families.

Because hospitals with fewer than 200 beds are unlikely to manage and treat patients with AATD, we can assume that the 22 AATD patients documented in this survey represented 91.86% of the total Japanese population. Therefore, statistical